Life course influences on cognitive ability and cerebrovascular disease

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To Jonathan, Samuel and Ruth

In my beginning is my end.

...In my end is my beginning.

T.S. Eliot, East Coker (1940)

Contents

Declaration

This thesis has been composed by myself, and the work is my own, except where acknowledgment is made by reference. The work in this thesis has not been submitted for any other degree or professional qualification.

Susan Deborah Shenkin, August 2005

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Abstract

This thesis aimed to investigate life course influences on cognitive ability and cerebrovascular disease (CVD) in older people. 110 community-dwelling subjects (70.0% female, mean age 78.2 (SD 1.4) years) born in Edinburgh hospitals between 1921 & 1926 had birth parameters (weight, length, placental weight) extracted from archives, underwent physical and neuropsychological tests, and imaging of brain volume, white matter lesions (WML) and diffusion tensor imaging (DTI).

(1) Relationship between cognitive ability and structural brain indices.

Cognitive ability (*g*) was associated with both whole brain volume ($r = .24$, $P < .05$) and intracranial area ($r = .27$, $P < .01$), suggesting the relationship between brain size and cognitive ability in old age is due to the persistence of this relationship from earlier life. WML correlated with MMSE ($\rho = -.21$, $P < .01$), and weakly correlated with fluid ($\rho = -.13$, $P > .05$) but not crystallised ability ($\rho = 0$), suggestive of cognitive decline due to WM damage. DTI is proposed as a sensitive marker of WM damage, especially in frontal regions (<D> and verbal fluency $r = -0.25$, $P = .009$).

(2) Relationships among early life factors (birth parameters, social class, the Apolipoprotein E *(APOE)* gene) and cognitive ability.

There was an association between birth weight and cognitive ability in old age (Raven's $r = .20$, $P = .04$; MMSE $\rho = .23$, $P = .02$), partly but not fully explained by this association in earlier life. Therefore, the prenatal environment may influence cognitive ability into old age. Social class correlated negatively with cognitive ability in childhood ($\rho = -.21$, $P = .02$) but not later life (Raven's $\rho = -.09$, $P = .36$): the influence of the shared environment decreases with time. *APOE*e4 was associated with worse performance on logical memory only ($t = -2.2$, $P = .03$), suggesting this genetic influence on cognitive ageing may be specific to memory.

(3) Relationships among early life factors and CVD.

Birth parameters, particularly placental weight, were associated with a history of CVD ($t = -2.2$, $P = .04$), WML load ($\rho = -.23$, $P = .04$), and DTI (<D> $r \sim -.25$, $P = .03$, FA frontal $r = .36$, $P = .001$), suggesting placental function may be important for the development and integrity of WM tracts. There was no association between either social class or *APOE*e4 and CVD.

Therefore, in this cohort there were small but distinct early life influences on cognitive ageing and CVD respectively.

Publications arising from this thesis

Shenkin SD, Bastin ME, MacGillivray TJ, Deary IJ, Starr JM, Rivers CS, Wardlaw JM. Cognitive Correlates of Cerebral White Matter Lesions and Water Diffusion Tensor Parameters in Community Dwelling Older People. *Cerebrovascular Diseases* 2005; 20: 310-318.

Shenkin SD, Starr JM, Deary IJ. Birth Weight and Cognitive Ability in Childhood: a Systematic Review. *Psychological Bulletin* 2004; **130 (6):** 989-1013.

Shenkin SD, Bastin ME, MacGillivray TJ, Deary IJ, Starr JM, Wardlaw JM. Childhood and current cognitive function in healthy 80-year-olds: a DT-MRI study. *Neuroreport* 2003; **14 (3):** 345-351

Shenkin SD, Starr JM, Pattie A, Rush MA, Whalley LJ, Deary IJ. Birth weight and cognitive function at age 11 years: results from the Scottish Mental Survey 1932. *Arch Dis Child* 2001; **Sep; 85(3)**:189-196.

These are reproduced in Appendix 9.1.

List of abbreviations

ABC	Aberdeen Birth Cohort
ABPI	Ankle brachial pressure index
ADC	Apparent diffusion coefficient (DWI parameter)
ALIC	Anterior limb internal capsule
APOE	Apolipoprotein E gene
BG	Basal ganglia
BMI	Body mass index (weight (kg) / height^2 (m^2))
BP	Blood pressure
BW	Birth weight
CaVD	Cardiovascular disease
CC	Corpus callosum
CHI	Community Health Index
CI	Confidence Interval
CS	Centrum semiovale
CT	Computerised Tomography
CVD	Cerebrovascular Disease
<D>	Mean diffusivity (DTI parameter)
DTI	Diffusion tensor imaging
DWI	Diffusion weighted imaging
DWMH	Deep White Matter Hyperintensities
df	Degrees of freedom
FA	Fractional anisotropy (DTI parameter)
FLAIR	Fluid-attenuated inversion recovery (MRI)
FSE	Fast spin echo (MRI)
g	general cognitive factor
GA	Gestational age
GP	General Practitioner
HADS	Hospital anxiety and depression scale
ICA	Intracranial area
ILA	Ischaemic leukoaraiosis

IMT	Intima media thickness (carotid artery)
ISD	Information and Statistics Division (Common Services Agency)
LBC	Lothian Birth Cohort
LMP	Last menstrual period
MCI	Mild cognitive impairment
MHT	Moray House Test
MMSE	Mini-mental State Examination
MRI	Magnetic Resonance Imaging
NART	National Adult Reading Test
NIDDM	Non-insulin dependent diabetes mellitus
PVH	Periventricular Hyperintensities
PVWM	Periventricular white matter
PLIC	Posterior limb internal capsule
RMSMH	Royal Maternity and Simpson Memorial Hospital
ROI	Region of interest
RSPM	Ravens Standard Progressive Matrices Test
RT	Reaction time
RTM	Reitan Trail Making Test
SCRE	Scottish Council for Research in Education
SD	Standard deviation
SDMT	Symbol Digit Modalities Tests (test of processing speed)
SMS	Scottish Mental Survey
TIA	Transient ischaemic attack
VCI	Vascular cognitive impairment
VF	Verbal Fluency (test of executive function)
WBV	Whole brain volume
WCST	Wisconsin Card Sorting Test (test of executive function)
WML	White matter lesions
WTCRF	Wellcome Trust Clinical Research Facility
ρ	Spearman's rho
X^2	Chi-squared

1 Introduction

Populations in Western society are ageing, with both an increasing mean age, and increasing proportion of older people. For example, in Scotland, between 2000 and 2031 the number of people aged over 65 years is expected to increase from 787,000 to 1,200,000, and those over 85 years from 84,000 to 150,000. The proportion of those over 65 years has increased in the last century, and is projected to increase from the current proportion of under 20% to 22-24% by 2016 (Scottish Executive, 2002). The single most feared aspect of growing old is probably cognitive decline (Martin, 2004), with around 5% of people over 65 years and 25% of over 85 years suffering from dementia (Scottish Executive, 2002). Cognitive impairment affects a much larger proportion of the population than this, as there is a spectrum of cognitive decline from dementia to normal cognitive ageing. The terms mild cognitive impairment (MCI) (Petersen et al., 2001) or cognitively impaired, not demented (CIND) (Ebly, Hogan, & Parhad, 1995) have been introduced to describe decline prior to Alzheimer's disease, and vascular cognitive impairment (VCI) for cognitive decline due to cerebrovascular disease (Bowler & Hachinski, 1995). There is a need for increased understanding of the cerebral basis for age-related cognitive decline to improve the health of older people (National Research Council, 2000). Early cognitive impairment due to cerebrovascular disease is particularly important to recognise because it is common - 78% of elderly individuals coming to autopsy have evidence of cerebrovascular disease (2001) - and there is the potential for intervention to target vascular risk factors (Bowler & Hachinski, 2003).

The increasing elderly population has led to an increase in the prevalence of chronic diseases, particularly vascular disease, in the developed world. Traditionally, the risk of these diseases was attributed to adult risk factors such as smoking or obesity, but recently there has been a resurgence of interest into the concept that health and disease in later life, has its origins in early exposures, even while the individual is developing in the womb (Barker, 1998; Lucas, Fewtrell, & Cole, 1999; Langley-Evans, 2004). These influences may act into old age (Sayer, Cooper, & Barker, 1997; Sayer & Cooper, 2004). Initially this research focussed on the importance of prenatal

influences, and was described as *the Fetal Origins of Adult Disease* Hypothesis (Barker, 1994; Barker, 1998), but it is now acknowledged that postnatal exposures are also important, and that early life exposures can affect both the risk of disease and have an impact on health. Therefore, studies in this area now use the term *Developmental Origins of Health and Disease* (Barker, 2004). Many researchers acknowledge that a distinction between early and late life is artificial, and adopt a *life course approach* (Kuh, Ben Shlomo, Lynch, Hallqvist, & Power, 2003; Kuh & Ben-Shlomo, 2004a), acknowledging the cumulative importance of exposures from conception to old age.

This thesis is concerned with life course influences on cognitive ageing and associated cerebrovascular disease in a cohort of older people (aged 75-81 years) born in Edinburgh hospitals from 1921-1926. These individuals occupy the mild end of the spectrum from normal cognitive ageing to dementia.
The aims of this thesis are to investigate, in this cohort,
(1) the relationship between cognitive ability and structural brain indices (volume, white matter lesions and diffusion tensor imaging parameters);
(2) the contribution of early life factors to cognitive ability by investigating relationships among birth parameters (weight, length, placental size), social class, the Apolipoprotein E (*APOE*) gene and cognitive ability; and
(3) the contribution of early life factors to cerebrovascular disease by investigating relationships among birth parameters (weight, length, placental size), social class, *APOE* and cerebrovascular disease (CVD). CVD is defined by subjects' self-report, vascular risk markers and neuroimaging variables.

In this introduction, the literature on cognitive ageing is briefly reviewed (Chapter 1.1). Changes in cognitive ability with age are described, followed by the structural brain changes seen with ageing. Potential mechanisms for a relationship between brain structure and cognitive change are discussed. This includes a detailed review of the literature on diffusion tensor imaging and cognitive ability. The *Developmental Origins of Adult Health and Disease* hypothesis is then introduced (Chapter 1.2), and the evidence relating early life exposures to later life cognitive ability and

cerebrovascular disease is reviewed. Finally, the importance of considering early life influences in a life course perspective is discussed (Chapter 1.3). This includes the importance of genetic as well as environmental influences, and genetic influences on both cognitive ability and cerebrovascular disease are discussed using the example of *APOE*.

1.1 Cognitive ageing

1.1.1 Changes in cognitive ability with age

1.1.1.1 What is cognitive ability?

Investigation of changes in cognitive ability with age first requires an understanding of the construct of cognitive ability. The term 'cognitive ability' is used in this thesis, but literature in this area uses many similar terms (cognitive function(s), mental ability, mental function, intelligence, IQ) almost interchangeably. 'Intelligence' generally refers to psychometric intelligence, the human differences measured by cognitive ability (mental) tests (Deary, 2001b). One definition, presented in a consensus statement of 52 well-known researchers published in the Wall Street Journal as well as an editorial in *Intelligence* is

> "Intelligence is a very general mental capacity that, among other things, involves the ability to reason, plan, solve problems, think abstractly, comprehend complex ideas, learn quickly and learn from experience. It is not merely book learning, a narrow academic skill or test-taking smarts. Rather it reflects a broader and deeper capability from comprehending our surroundings – 'catching on', 'making sense' of things or 'figuring out' what to do." (Gottfredson, 1997) (p13).

Intelligence has been measured using numerous different tests, and it is remarkable that, almost irrespective of the tests used, there is a general cognitive factor (*g*) common to many different cognitive tests that accounts for about 50% of the total variance when a varied battery of mental tests is administered to a normal adult population sample (Neisser et al., 1996). The general cognitive factor (*g*) was first described by Spearman in 1904, and has been replicated in several large datasets of representative populations (Deary, 2000b). General cognitive factors from different batteries of mental tests show very high correlations (over 0.9) (Johnson, Bouchard, Jr., Krueger, McGue, & Gottesman, 2004).

There is more to cognitive ability than general intelligence (*g*). The best-agreed taxonomy of human ability differences was proposed by Carroll (Carroll, 1993) who re-analysed over 400 sets of data of mental ability tests. Using factor analysis, he determined that a three stratum model best fitted the data. At the top of the hierarchy (stratum III) is general intelligence (*g*). At stratum II there are eight broad types of mental ability (crystallised intelligence, fluid intelligence, general memory and learning, processing speed, broad cognitive speediness, broad retrieval ability, broad auditory perception and broad visual perception), and at stratum I the very specific mental abilities (e.g. vocabulary, block design, digit-symbol coding, digit span). The actual number of abilities in each stratum varies between studies, but there is general agreement that most data sets conform to a three stratum model, with *g* at the top, then secondly group factors (most commonly verbal, spatial, memory and processing speed) and finally specific mental abilities (Deary, 2000b).

The general cognitive factor (*g*) has been shown to be a reliable and valid measure of success in education and occupation, including military training. For example, there is a correlation between *g* and job success of around 0.5 (Schmidt & Hunter, 1998). Although this correlation is moderately strong, indicating that cognitive ability is important, there are evidently other factors that contribute to job success.

Similarly, some researchers have focussed on the large proportion of variance in cognitive ability explained by *g*, without emphasising the substantial proportion it leaves unexplained (e.g. (Jensen, 1998)). There has been controversy surrounding the concept of *g*, and some researchers have dismissed *g* as a statistical artefact (Gould, 1981), or focussed on alternative, multiple intelligences (Gardner, 1999). However, repeated analyses using factor analytic or structural equation modelling techniques find that the hierarchical structure is the best fit to the data (Gottfredson, 2001; Gottfredson, 1997), and this is accepted by the majority of researchers (Neisser et al., 1996).

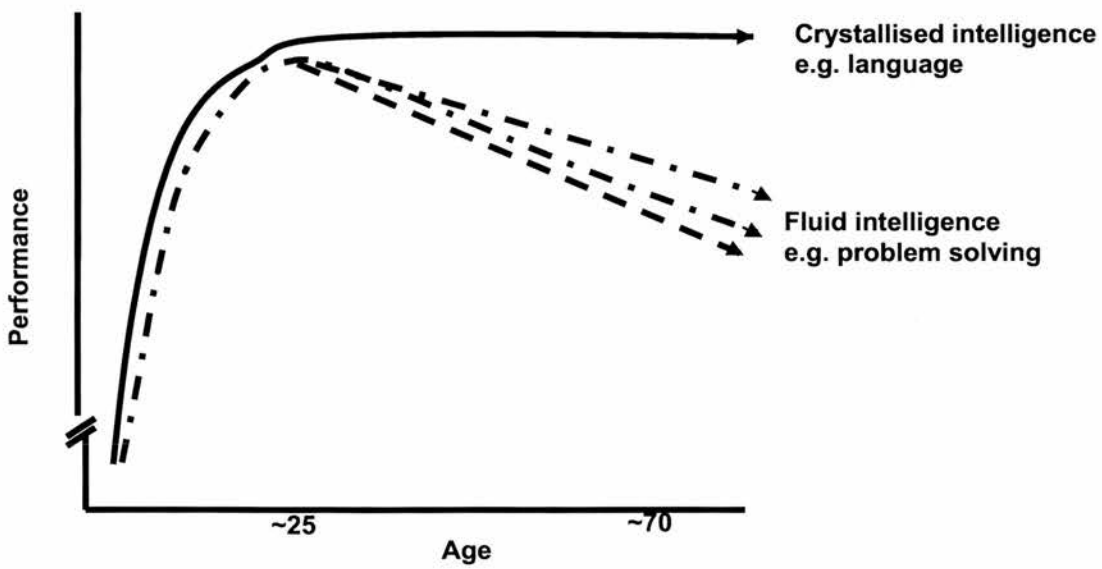
If it is acknowledged that the hierarchical description of intelligence is a taxonomy describing human intelligence differences, rather than attempting to explain them,

then this structure can provide a useful basis for research into the underlying mechanisms of individual differences. The levels can be seen as "target pools of variance (general to specific) for explaining by investigations which inquire about the origins of variation in human mental abilities" (Deary, 2001a) (p. 128). Therefore, research into biological correlates of cognitive ability differences can target any of these levels to try to increase understanding of the underlying mechanisms. In this thesis both *g* and specific cognitive abilities are used as targets.

1.1.1.2 How does cognitive ability change with age?

In the psychometric study of cognitive ageing, two concepts are important. Firstly, the distinction between crystallised and fluid intelligence, and secondly the role of processing speed. The distinction between crystallised (Gc) and fluid (Gf) intelligence was made by Cattell (1963) (in Deary, 2000b), who proposed that intelligence was made up of these two main components. He suggested that Gc reflected knowledge acquired throughout life and stayed stable over the lifespan. Gf, however, was biologically determined, and declined from early adulthood (Fig 1.1).

Figure 1.1: Representation of changes in crystallised and fluid intelligence with age (after Deary, 2000b). Three possible trajectories of fluid intelligence to illustrate individual differences.



The graph shows three possible trajectories to illustrate that there are marked individual differences in the rate of cognitive decline with age. Crystallised type abilities are vocabulary, general knowledge and some number skills. These stay relatively constant in healthy ageing and even into early dementia (McGurn et al., 2004). Fluid type abilities tend to show decrements with age, although people who score well earlier in life will still tend to score better on later tests (Schwartzman, Gold, Andres, Arbuckle, & Chaikelson, 1987). These tasks typically require abstract reasoning, particularly under time pressure, with new materials, where previous experience provides no advantage. Memory, processing speed and reasoning tasks also decline with age (Deary, 2000b). This theory predates Carroll's factor analyses which produced the hierarchical structure described above. Gf and Gc are included in stratum II, and are the two factors that correlate most closely with *g,* as well as correlating closely with each other.

Secondly, there is an important role in cognitive ageing for the speed of information processing (Salthouse, 1996). This tends to be assessed with paper-and-pencil tests such as the timed Digit Symbol Substitution Test from the WAIS, or computer based measures of inspection or reaction time (Salthouse, 2000; Deary, 2000b). With increasing age, speed of processing slows, and this accounts for much of the age-related decline in all cognitive domains. For example, a meta-analysis of age-speed correlations for perceptual speed and reaction time showed a weighted average correlation of around 0.5 (Verhaeghen & Salthouse, 1997). Information processing starts to slow as early as the 20s (Deary & Der, 2005). Age is inversely correlated with *g:* as age increases performance on most tests decline together. However, performance on fluid type tests will tend to decrease more than crystallised type tests (Wilson et al., 2002). Once the effect of age on *g* is taken into account, there is little residual effect of age on more specific abilities (Salthouse, 1996), although more recent research now suggests that there may be additional age effects on, for example, memory, distinct from *g*. Salthouse now proposes at least three distinct types of age-related influence on cognition: age, speed of processing and memory (Salthouse & Ferrer-Caja, 2003). Thus, processing speed might be a cognitive aspect that accounts for some of the ageing in other mental functions, and understanding the biological basis of this processing speed will further the understanding of cognitive

ageing (Salthouse, 2000; Deary, 2001b). To understand the biological basis of ageing requires an understanding of structural brain changes with age, which is reviewed below in Chapter 1.1.2.

1.1.2 Changes in brain structure with age, and relationship to cognition

In this section the major brain structural changes with age – atrophy and cerebrovascular disease, particularly the accumulation of white matter lesions (WML) - are outlined. The evidence for a relationship between these factors and cognitive ability is reviewed briefly. The importance of vascular risk factors is discussed. There follows a detailed review of the technique of diffusion tensor imaging (DTI) as a measure of white matter integrity. The relatively small literature concerned with changes in DTI parameters with age are reviewed in detail, with particular emphasis on studies of cognitive ageing.

1.1.2.1 Atrophy

Pathological studies

Autopsy studies show a decrease in fresh weight of the brain with age. The maximum weight is attained at about 20 years of age, remaining constant until 40 -50 years, then declining at around 2-3% per decade, reaching around 90% of maximum at 80 years (Mann, 1998). Some people will show substantial atrophy, some much less, and it can be difficult to distinguish whether this is due to the normal ageing or associated neurodegenerative diseases (Mueller et al., 1998). The cortex, at the surface of the brain, is composed of grey matter, mostly cell bodies and nerve fibres, thrown into gyri, or folds. The subcortical white matter consists largely of myelinated nerve fibres. As the brain reduces in size, shrinkage of the gyri is evident, and there is an associated increase in the cerebrospinal fluid surrounding the brain, and in the lateral ventricles (Snell, 1986). Skull size is fixed at around age six and stays constant throughout life, therefore with age there is a decrease in the ratio between brain size and intracranial capacity (skull volume) (Gale, Walton, & Martyn, 2003). The amounts of both grey and white matter decrease with age, with grey matter being preferentially lost from age 20-50 years, but the majority of atrophy in later life (50 years+) is due to white matter loss: a decrease in myelinated

fibres and an increase in extracellular space (Harris et al., 1994; Nusbaum, Tang, Buchsbaum, Wei, & Atlas, 2001).

The decrease in brain weight with age led to the assumption that there was a corresponding decrease in brain cell (neurone) number (Mann, 1998). However, this now appears to be an artefact in the methodology used to count neurones (Flood & Coleman, 1988). Studies to date do show evidence of neuronal loss in normal ageing (e.g. Tang, Nyengaard, Pakkenberg, & Gundersen, 1997) but this is much smaller than previously thought (in the order of 10%), and insufficient to explain the extent of brain atrophy (Morrison & Hof, 1997; Tang et al., 1997). An alternative explanation could be shrinkage of the nerve cell body or its processes (axons and dendrites) (Hedden & Gabrieli, 2004), or activation of microglia, and possibly phagocytosis of myelin (Sheng, Mrak, & Griffin, 1998).

Does ageing affect the whole brain or specific regions? There is some evidence for regional rather than global atrophy with age, particularly in frontal and temporal regions (Flood et al., 1988) but most studies have found an association between atrophy in specific brain regions and neuropathology rather than normal ageing. For example, atrophy of the medial temporal lobe and hippocampus has been associated with Alzheimer's disease (Morrison et al., 1997; Mann, 1998). It may be, therefore, that global atrophy is a feature of normal ageing, and brain regional atrophy more indicative of pathology.

Neuroimaging studies

Imaging studies allow non-invasive measurement of in vivo brain volume. A review of 12 cross-sectional studies of brain volume changes with age (*n* from 49 to 2,081, mean age from 21 to 62, range 18 to 97 years) shows a decline in whole brain volume normalised for intracranial volume from 89% at age 20 to 78% at age 80 (median decline 0.23% per year, range 0.15 to 0.28%) (Fotenos, Snyder, Girton, Morris, & Buckner, 2005; DeCarli et al., 2005b). However, cross-sectional studies are limited as they cannot truly describe change with age: they may be describing differences in older age brain structure in people born at different times due to

'cohort effects', i.e. differences in the environment during development rather than ageing causing differences between older and younger cohorts (Hennekens & Buring, 1987). Longitudinal studies minimise these effects, and mean that an individual acts as his own baseline, therefore reducing between-subject variance. They are, however, more difficult to perform than cross-sectional studies, particularly in studies of ageing, due to loss to follow-up. Large numbers of participants are therefore required, and this is costly. There is also a large investment of time: few researchers can develop studies to follow participants throughout the decades of ageing (Ebrahim, 1996). Seven longitudinal studies have documented annual whole brain volume change in non-demented older people of around -0.5% (95% Confidence Intervals -0.37 to 0.88%) (Jack, Jr. et al., 2004; Liu et al., 2003; Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003; Chan et al., 2001; Wang et al., 2002; Thompson et al., 2003; Fotenos et al., 2005), although one showed -2.1% (Raz et al., 2004). This discrepant result may be due to different inclusion criteria or technical differences such as scan resolution. Furthermore, technology may change over time, affecting methods of acquiring and analysing images, thus making comparisons between different time points difficult.

Of particular value are studies that compare cross-sectional and longitudinal methodology. Many of these studies investigate changes related to dementia. The control groups in these studies show changes in normal ageing. Fotenos et al. (2005) imaged 370 adults cross-sectionally, then 79 of those aged over 65 years longitudinally (mean 1.8 years later). 127 were 'young' (mean age 23, SD 3 years), 51 'middle aged' (mean age 50, SD 8 years) and 192 'old' (mean age 78). Of the 'old' group 94 were non-demented (using the Clinical Dementia Rating scale). Both cross-sectional and longitudinal studies showed whole brain atrophy beginning in early adulthood, and accelerating at around age 44 (cross-sectional correlation between age and whole brain volume (WBV) r = -.88, lifespan atrophy -.23% per year). There was an increase in the variability of WBV measures as age increases. Longitudinally, the WBV atrophy rate was -.45% (95% CI -1.49 to .59%) per year in non-demented individuals (n = 43). This compares with the cross-sectional estimate of -.31 to -.46% in those aged 65 to 95. This study showed good agreement between

cross-sectional and longitudinal results, suggesting that secular effects and other confounds minimally affect WBV cross-sectional estimates, although the relatively short follow-up and small numbers mean that further studies are required.
Studies vary in their results as to whether there is a sex difference in brain atrophy. If brain size is corrected for head size, some studies show men declining slightly faster than women (e.g. Raz et al., 2004), some show women declining faster than men (e.g. Resnick et al., 2003) and some show no difference (Liu et al., 2003; Fotenos et al., 2005). The discrepancies between these results may be due to methodological differences (including methods of normalising brain volumes), and health differences between cohorts.

Neuroimaging studies have also shown that ageing predominantly affects white matter (Nusbaum et al., 2001). Some studies have shown a decline in white matter volume after the age of 70 (see Pfefferbaum et al., 2000), whereas others suggest that there is little volume change, but that microstructure degrades with age (see Sullivan et al., 2001). Magnetic resonance spectroscopy studies indicate that grey matter remains viable and relatively resilient to ageing (Pfefferbaum et al., 2000).

Neuroimaging studies have investigated whether ageing affects whole brain volume or regional volumes. The largest study to date of 2,081 participants in the Framingham Heart Study (DeCarli et al., 2005b) showed that age explained around 50% of whole cerebral brain volume differences, with little age-related change before age 50. Frontal lobe volumes showed the greatest decline with age, with smaller differences for temporal lobes. Relative loss of frontal lobe volume has been confirmed in longitudinal studies (Resnick et al., 2003).

Imaging studies show a higher rate of atrophy than pathological studies. This may be due to methodological limitations of examining post mortem brains, including difficulty in accounting for ventricular volume. The true description of changes with ageing is limited by the available methodology: post-mortem studies are prone to fixation artefact, but in vivo studies rely on the sensitivity of imaging technologies (Pfefferbaum et al., 2000).

This section has summarised pathological and neuroimaging showing that, from around middle age, there is generalised brain atrophy particularly of the white matter, probably due to the shrinkage of nerve cells bodies or processes. This may be more prominent in the frontal lobes. The relationship between brain atrophy and the cognitive changes that occur with age is now considered.

Atrophy and Cognitive Ageing

Historically, there has been much interest in correlating brain size with intelligence (Deary, 2000b). Before accurate measures using neuroimaging techniques were possible, head size was used as a proxy for brain size, and there was a small, but statistically significant, association between head size and intelligence: in adults a mean correlation of around 0.15 (Wickett, Vernon, & Lee DH, 2000). The size of the skull vault reflects the maximum size of the brain, and is attained by around age six years (Gale et al., 2003), and the correlation between head size and cognitive ability reflected maximal rather than current brain size. Head size is closely related to brain size, but these cannot be seen as equivalent, particularly in the elderly, where brain size (but not head size) will change with ageing related cerebral atrophy. However, some studies have correlated head size and cognitive ability in older people. Reynolds et al. found an association between small head circumference and low MMSE score (Reynolds, Johnston, Dodge, DeKosky, & Ganguli, 1999). For every 1 cm increase in head size the probability of an MMSE in the lowest 10% decreased by 20%. Tisserand et al. found that people with smaller heads scored less well on tests of intelligence, global cognitive functioning, and speed of information processing (r = .07 to .21), but not memory (Tisserand, Bosma, Van Boxtel, & Jolles, 2001). These studies did not account for prior cognitive ability. This is important because differences in cognitive ability in old age may be due to the stability of these differences from earlier in life, rather than a decline due to age (Deary, Whalley, Lemmon, Crawford, & Starr, 2000).

The use of neuroimaging to measure actual whole brain volume is a much more accurate measure of actual brain size than proxy measures such as head size. In

neuroimaging studies, there is a consistently documented moderate correlation between brain size and cognitive ability in young adulthood. A meta-analysis of *in vivo* brain volume and intelligence reviewed 37 independent samples (n = 1,530), and found a correlation between brain volume and intelligence of 0.33 (McDaniel & Nguyen, 2002). Twenty-four of the studies were in adults (r = .41 for females, r = .38 for males, .33 for sexes combined), but the mean age was not reported. There is little evidence whether this relationship persists into old age (see below), but neuroimaging, unlike head size, studies can allow for changes in brain size relative to head size (atrophy).

One well-powered study of 97 unmedicated healthy elderly men (mean age 67.8 SD 1.3 years) found intracranial area (an estimate of maximal brain size (Ferguson, Wardlaw, Edmond, Deary, & MacLullich, 2005)) and several regional brain volumes correlated with tests of premorbid and fluid intelligence and tests of visuospatial memory (r = .20 to .32) (MacLullich et al., 2002). The relationships between specific cognitive tests and regional brain volumes were best summarized by a significant positive relationship between the latent traits of a general brain size factor and a general cognitive factor (*g*) (structural equation modelling, correlation = .42) and not by associations between individual tests and particular brain regions. Therefore, in healthy elderly men, the relationship between brain region volume and cognitive ability may be largely due to longstanding associations between general cognitive ability and overall brain size. Conversely, however, results of one study of 106 subjects aged around 80 years (the Aberdeen Birth Cohort 1921) which were summarised in the meta-analysis (McDaniel, 2005) did not find a significant relationship between brain volume and cognitive ability (r = -.08). These results have not been published to date.

In summary, ageing is associated with both generalised brain atrophy, and changes in cognitive ability – a relative preservation of crystallised-type and decline in fluid-type intelligence (see Chapter 1.1.1.2). Brain size is associated with cognitive ability in adulthood, and it has been suggested that the relationship between brain size and

cognitive ability in old age is due to the persistence of this relationship from earlier life. There is, however, a need for further studies to investigate this.

1.1.2.2 Cerebrovascular disease

In addition to volume loss with age, the other major change in the brain which has been described with age is the impact of cerebrovascular disease (CVD). Occlusion of large and small cervical and intracranial arteries increases with age, causing stroke. More subtle changes in the brain with age are also thought to have a vascular aetiology, namely white matter lesions (WML or leukoaraiosis). The pathological and neuroimaging evidence of WML and their association with age and cognitive ability is presented below.

Pathological studies

Classical cerebrovascular disease includes large infarcts which affect the cortex, and to varying degrees the underlying white matter (Munoz, 2003). These are mostly related to tissue anoxia secondary to atherosclerosis or systemic embolism, although there are rarer causes. The more subtle changes of white matter lesions (or abnormalities or hyperintensities) were first described in pathological studies by Binswanger in 1894 as lacunes and *état criblé* (see Roman, 1996). Macroscopically, there is preservation of the cortex, but subcortically there is patchy discoloration of the white matter. There is substantial loss of axons and their myelin sheaths, associated with reactive astrocytosis and loss of oligodendroglial cells (Mann, 1998).

The pathogenesis of white matter lesions (WML) is still under debate, although the most common theory is ischaemic demyelination due to stenosis or occlusion of small perforating arteries (DeCarli, Fletcher, Ramey, Harvey, & Jagust, 2005a; Wardlaw, Sandercock, Dennis, & Starr, 2003). White matter is vulnerable to ischaemia for three main reasons. Firstly, cerebral white matter is a 'terminal field' where systemic hypotension will cause relatively lower blood flow than the rest of the brain. Secondly, blood vessels supplying white matter lack anastamoses with other blood vessels. Thirdly, arteriosclerotic changes in cerebral blood vessels mean they cannot withstand blood pressure fluctuations, causing subtle white matter changes such as selective cell death (Sarti & Pantoni, 2003). These small vessel

changes cannot only affect white matter directly, but can also damage the blood brain barrier, increasing the delivery of vasoactive substances. Alternatively, breakdown of the blood-brain barrier may be the primary mechanism for WML development (Wardlaw et al., 2003). It is likely that blood-brain barrier damage and ischaemia are complementary, as both have a common substrate in hypertension and small vessel changes.

Neuroimaging studies

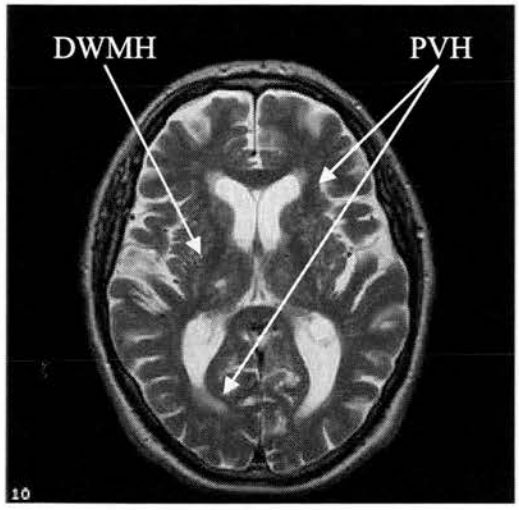
The concept of WML was derived from imaging rather than histopathology, as a descriptive term for hypodense subcortical areas on Computerised Tomography (CT) scans (Hachinski, Potter, & Merskey, 1987). Advances in neuroimaging increased the detection of white matter changes, best identified on T2-weighted, fluid-attenuated inversion recovery (FLAIR), and proton density Magnetic Resonance Imaging (MRI). Changes that are manifest on MRI may not be seen on gross examination, and dismissed as post-mortem artefact at microscopy (Munoz, 2003).

The prevalence of WML increases with age, (Longstreth, Jr. et al., 1996). For example, in the Cardiovascular Health Study, 1,919 participants aged over 65 years underwent MRI scans 5 years apart. 84% of participants showed some evidence of WML, and 28% of scans worsened over 5 years (Longstreth, Jr. et al., 2005). WML have functional consequences, and are associated with many ageing-related conditions e.g. impaired balance and gait, (Breteler et al., 1994; Starr et al., 2003) depression, hypertension (Fazekas, Chawluk, Alavi, Hurtig, & Zimmerman, 1987), transient ischaemic attack or stroke (Longstreth, Jr. et al., 1996; Vermeer et al., 2003a), reduced respiratory function (Liao et al., 1999), as well as cognitive impairment (Gunning-Dixon & Raz, 2000).

The extent and intensity of WML are important as they reflect the degree of underlying tissue damage (Scheltens, 2003). This has led to a proliferation of visual rating scales that estimate the extent and severity of WML (e.g. Fazekas et al., 2002; Wahlund et al., 2001; Scheltens, Erkinjuntti, Leys, & et al., 1998). Most MRI visual

rating scales distinguish between deep white matter hyperintensities (DWMH) and periventricular 'caps' and 'rims' (PVH) (Scheltens et al., 1998) (Figure 1.2).

Figure 1.2: T2-weighted MRI scan showing Deep White Matter Hyperintensities (DWMH) and Periventricular Hyperintensities (PVH)



DWMH and PVH are thought to have different aetiologies and functional consequences (Schmidt et al., 2004), but see (DeCarli et al., 2005a). DWMH probably have a vascular origin (Schmidt et al., 2004) whereas PVH may be due to disruption of the ependymal lining with subependymal gliosis and myelin degradation (Leaper et al., 2001; Schmidt et al., 2004). In general, however, evidence from anatomical, histopathological, clinical and experimental studies suggests that all WML have an ischaemic aetiology, showing vascular fibrosis and lipohyalinosis (DeCarli et al., 2005a). This proposed ischaemic aetiology of WML and their rapid progression has led to the suggestion that WML could be used as a surrogate endpoint in clinical trials of cerebral small-vessel disease which currently use primary outcome measures of cognitive impairment and dementia (Schmidt et al., 2004).

Vascular risk factors

WML have been associated with typical vascular risk factors: arterial hypertension, cigarette smoking, history of vascular disease, diabetes mellitus and carotid atheroma (Hill & Bisognano, 2005; van Gijn, 2001; Ott et al., 1999). Furthermore, there is a suggestion that improved blood pressure control may reduce the development of

WML (Dufouil et al., 2001). In studies considering cerebrovascular disease, including WML, it is therefore important to take account of major vascular risk factors. In this study all factors mentioned above were measured (smoking history, medical history, and measures of atheroma both in carotid arteries and peripheral (ankle) vessels).

Non-invasive measures of atheromatous load are useful outcome measures in studies of vascular disease. Two measures are used in the Simpson's study: (1) lower limb using ankle-brachial pressure index (ABPI) (Fowkes, 1991) and (2) extracranial carotid arteries using duplex ultrasonography (Grobbee & Bots, 1994). Carotid atherosclerosis can be measured as proportion of the lumen occluded, or intima-media thickness (IMT) in the common carotid artery. ABPI, CIMT and carotid artery stenosis have all been associated with cerebrovascular events and WML on MRI scans (Bots et al., 1993; Bots, Hoes, Koudstaal, Hofman, & Grobbee, 1997). ABPI measurement and carotid ultrasonography are well-established techniques, and the results have been found to accurately reflect underlying atheroma.

This section has summarized pathological and neuroimaging studies showing that WML accumulate with age, and probably have an ischaemic aetiology. WML are associated with vascular risk factors and various physical and psychological outcomes. The relationship between WML and cognitive ability is considered below.

Brain white matter lesions and cognitive ageing

An association between cerebrovascular lesions and cognitive change has long been acknowledged, initially termed 'vascular dementia' (Bowler et al., 1995), but now redefined as 'vascular cognitive impairment' (VCI) (2003). This is because the definition of dementia focussed on a gradual decline, and cognitive impairments prominent in dementia of Alzheimer's type (such as memory). This meant that patients with significant impairments due to vascular disease did not reach diagnostic criteria if deterioration was sudden, such as after a stroke, and predominantly affected other cognitive domains. The concept of VCI encompasses all causes of cerebrovascular disease and all levels of cognitive decline. Thus, patients can be identified earlier, allowing the potential for primary and secondary preventive

therapy. This thesis concentrates on the association between WML and cognitive ability in older people.

In patients with dementia, there is no consistent association between extent of WML and cognitive impairment, with some studies showing a correlation between degree of PVH and severity (Scheltens, 2003), and some finding no association (Leys et al., 1990; Starkstein et al., 1997). However, people with WML have an increased risk of dementia (Vermeer et al., 2003b), particularly if they have background cerebrovascular disease (Scheltens, 2003).

In normal cognitive ageing, the association between WML and cognitive function differs between studies. Even the highest powered studies show only a weak association with impaired performance on tasks of processing speed, executive function and memory, but no association with general intelligence measures (Hedden et al., 2004; Gunning-Dixon et al., 2000). A meta-analysis (Gunning-Dixon et al., 2000) of 21 studies including 4,476 subjects concluded that WML are associated with impaired performance when all cognitive indices were included in analyses (Fisher's z = .20, SD = .16). When specific cognitive domains were examined, increased WML score was associated with impairment on tests of processing speed (Fisher's z = .22, SD.13), memory (immediate (z = .12, SD.16) and delayed (z = .20, SD .10)), executive function (z = 31, SD .26) and indices of global cognitive function (z = .22, SD .19). There was a trend, but no statistically significant association between WML and psychometric indices of intelligence (fluid or crystallised) or fine motor performance. They did not distinguish between DWMH and PVH. This meta-analysis only included one large study (the Cardiovascular Health Study n = 3,301 (Longstreth, Jr. et al., 1996) which found an association between WML and global cognitive function (r = -.11) and processing speed (r = -.12). The other studies had a median n of 41, but there was no link between study size and strength of effect. Median age of participants was 69.15 years. Studies that used volumetric rather than semi-quantitative rating scales found larger effects, as did studies on younger subjects. Studies with more men tended to find larger effects. A large study not included in the meta-analysis, the Rotterdam Study (de Groot et al., 2000) (n = 1,077) found both WML and PVH were associated with lower performance on tests

of psychomotor speed memory and global cognitive function. The main effect was of PVH on processing speed: those with the highest severity of WML performed almost 1 SD below average for psychomotor speed, and 0.5 below average for global cognitive function.

Thus, there is evidence for a weak association between WML and cognitive ability (Vermeer et al., 2003b). Inconsistencies in the literature are probably due to the multifactorial aetiology of WML, and differences between studies in methodologies in image acquisition, scoring of WML and cognitive testing, as well as age of participants and extent of underlying disease. There is therefore a need for more sensitive measures of white matter integrity. One such technique is diffusion tensor MRI (DTI). The literature in this area is much less extensive and has not to date been summarised in systematic reviews or meta-analyses, therefore a detailed review of the studies describing DTI parameter changes with age, and how these changes relate to cognitive ability, is presented in Chapter 1.1.3 below.

1.1.3 White matter integrity: Diffusion Tensor MRI

Advances in magnetic resonance imaging (MRI) have allowed brain structures to be assessed in increasing detail. MRI itself was first described in 1943, and has only been in clinical use for about twenty years. Diffusion imaging was first described in 1985 (see Basser, 1995), and has only recently gained acceptance as a clinical tool. Diffusion weighted imaging (DWI) characterises the magnitude of water molecule diffusion in the brain, as they bounce off, cross, or interact with tissue components, such as cell membranes, fibres or macromolecules (Le Bihan, 2003). Clinical applications of DWI have included the identification of early tissue damage in brain ischaemia where water diffusion decreases acutely (Herneth, 2003), but although the apparent diffusion coefficient (ADC) derived from the DWI experiment provides sensitive measures of the amount of water diffusion, it does not give any information on its direction.

The technique of diffusion tensor magnetic resonance imaging (DTI) was first described about ten years ago (Basser, Mattiello, & LeBihan, 1994), and measures the magnitude and directionality of water molecule diffusion on a voxel by voxel

basis. It uses tensors - a mathematical construct used to describe multi-dimensional vector systems - to describe the restriction of water diffusion by white matter tracts. This goes beyond the traditional MRI assessment of morphology to allow examination of the tissue microstructure (Le Bihan, 2003; Sullivan & Pfefferbaum, 2003). DTI has been useful in various clinical settings including the assessment of stroke acutely (Roberts & Rowley, 2003), brain tumours (Bastin, Sinha, Whittle, & Wardlaw, 2002), demyelinating disease such as multiple sclerosis, epilepsy, and various neuropsychiatric disorders such as schizophrenia (Moseley, Bammer, & Iles, 2002), as well as investigating developmental changes in children (Prayer & Prayer, 2003).

Two scalar parameters are commonly computed to quantify the diffusion. **Mean diffusivity** (<D>) indicates the magnitude of water molecule diffusion in any direction (with the effects of anisotropy removed [see below]), whereas **fractional anisotropy** (FA) measures the coherence and orientation of diffusion (Basser & Pierpaoli, 1996; Pierpaoli, Jezzard, Basser, Barnett, & Di Chiro, 1996). In white matter tracts, water movement is restricted by axonal membranes and myelin, therefore areas containing intact neurones would be expected to have a low <D>, whereas areas where neuronal integrity is disrupted would have a high <D>. DWI studies typically measure diffusivity in three orthogonal directions to give the ADC, which is equivalent to <D> in DTI. DWI cannot, however, assess anisotropy.

If diffusion is equal in all directions it is said to be isotropic (from the Greek *isos* meaning equal and *tropikos*, meaning turning) (FA = 0). As directionality of diffusion increases, the diffusion is said to be anisotropic (FA increasing to 1). A measure of FA close to zero would be found in an area like cerebral ventricles which contain randomly diffusing cerebrospinal fluid (CSF); a low/medium value in grey matter where diffusion is restricted by cell membranes and organelles; whereas a measure close to one would be found in an area with regular, parallel white matter tracts such as the corpus callosum. Water is able to move more freely along the long axis of a tract rather than perpendicular to it. Increasing anisotropy is a likely measure, therefore, of white matter tract integrity. It should be noted that there are

numerous anisotropy indices, e.g. fractional anisotropy (FA), relative anisotropy (RA), lattice anisotropy (LA), volume ratio (VR), which differ significantly in accuracy, contrast, resolution and noise sensitivity (Li & Noseworthy, 2002). The most commonly used measure is FA, which is used here.

The assumption that the myelin sheath surrounding nerve fibres acts as the main barrier to water diffusion has led to the use of DTI to develop tractography: MR images of white matter tracts. This technique has great promise in understanding the connectivity and fibre organisation of white matter tracts, and their relation to function, although technical and computational limitations mean the images should be interpreted with care (Bammer, 2003). This has led to the possibility of investigating, in vivo, the theory of cortical "disconnection" (Geschwind, 1965; O'Sullivan et al., 2001a) as an underlying mechanism for age-related cognitive decline. These papers proposed that normal cognitive function is dependent on the integrity of large scale, integrated neurocognitive networks. If this integrity is compromised, e.g. by disruption of connecting white matter tracts, cognitive decline may result. Structural brain scans have investigated this by relating white matter lesions (WML) to cognition, finding only a weak association (Gunning-Dixon et al., 2000) (Chapter 1.1.2.2). This may be due to the multifactorial aetiology of WML, or the insensitivity of WML rating scales to the severity of underlying pathology (Fazekas et al., 2002).

DTI has therefore been proposed as a more sensitive measure of white matter integrity. Below, literature will be reviewed that investigates DTI changes in normal human ageing, and the associations between DTI parameters and cognitive ability in older people.

1.1.3.1 DTI parameters and normal ageing

The changes in brain structure and function with normal ageing (see Chapter 1.1.2) would suggest that we might expect <D> to increase and FA to decrease with age. In general, as described below and summarised in Table 1.1 and 1.2, cross sectional studies in healthy people with normal structural scans have shown this pattern.

Table 1.1: Studies of DTI and ageing

Study	n Old	n Young	Age Old	Young	Recruited from	ROI	Regions	DTI 'D'	'FA'	Result: D with age	Result: 'FA' with age
Head et al (2004) St Louis, MO, USA	25 28.0% men	25 48.0% men	69-88 mean 77 SD 5	19-28 mean 22 SD 2	Older : hospital dementia clinic Younger: students	Manual on anisotropy images	- CC - prefrontal - temporal - parietal - occipital - whole brain	D	A_σ (~ FA)	↑ all regions *frontal Ant>post CC $	↓ all regions *frontal Ant CC (not post CC) $
Madden et al. (2004) NC, USA	16 50% men	15 43-50% men	60-70 Mean 64.7	19-25 Mean 20.9	Healthy volunteers, community	Manual on tensor image	- CC - AL IC - frontal - visual	-	FA	-	↓ all regions *frontal
Pfefferbaum & Sullivan (2003) California, USA //	64 71.9% men		23-85 mean 52.5 SD 20		Healthy volunteers, community	Semi-automated on anatomical image	- CC - CS	D	FA	↑ all regions * CS CC: genu >splenium	↓ all regions *CS CC: genu >splenium
Abe et al. (2002) Tokyo, Japan	50 60% men		21-69 Mean 44.8 SD 14.0		Healthy volunteers, mostly hospital workers	Manual on anatomical image	- CC - frontal - parietal - LN - PLIC - thalamus	ADC	-	↑ trend all regions except PLIC *frontal *LN	-
O'Sullivan, Jones et al. (2001) London, UK	19 68.4% men	10 60% men	56-85 mean 72 SD 8	23-37 mean 30 SE 5	Older: research unit & GP Younger: staff	Semi-automated on FA	WM of one hemisphere: - anterior - middle - posterior	D	FA	↑ *frontal frontal>middle>post (NS) $	↓ *frontal frontal > middle > posterior (NS) $
Chen et al. (2001) Stockholm, Sweden	54 55.5% men		20-79		Normal from community	Histogram of whole brain <D>	- Whole brain: global, tissue	orientation-independent ADC	-	↑	-

Nusbaum et al. (2001) New York, USA	20 65% men		20-91 Media n 55		? Healthy volunteers	Histogram of whole brain <D>; voxels which correlate with age	Whole brain - structures identified anatomically if decreased FA	Whole brain ADC histo-gram	RA	↑ whole brain $	↓ frontal genu, splenium parietal PVWM $ ↓ occipital PVWM ↑ PLIC
Stebbins et al. (2001) abstract California, USA	10	10	Mean 80.4 SD 5.7	Mean 28.9 SD 3.5 Matched	Healthy, highly educated	NR	? - CC - frontal - posterior - BG	-	FA	-	↓ frontal> genu>BG Not posterior $$
Chun et al. (2000) New York, USA	38 52.6% men		26-86 mean 53.4 SD 17.0		11 healthy volunteers 27 patients	Histogram of whole brain <D>; ROI of perivent WM and thalamus	- whole brain - PVWM - thalamus	BD_{av}	-	-↑ whole brain ↑ PVWM not thalamus	-
Virta et al. (1999)	10 50% men	10 50% men	24-36 Mean 29.5	64-76 Mean 69.2	Healthy volunteers	Manually on anisotropy maps	- cerebral peduncle - pons - medulla	Trace (D)	LA	↓ peduncle, pons, medulla	↓ peduncle (not pons, medulla)

// includes 49 people from (Sullivan et al., 2001), which includes 13 men from (Pfefferbaum et al., 2000).
* = area most affected
$ = same result from comparison of old and young group
$$ = result only from comparison of old and young group (i.e. no correlation reported)

NR = not reported

ROI = region of interest (method for determining region of interest)
ADC = apparent diffusion coefficient
FA = fractional anisotropy
RA = relative anisotropy
LA = lattice anisotropy

PVWM = periventricular white matter
CC = corpus callosum
PLIC = posterior limb internal capsule
ALIC = anterior limb internal capsule
CS = centrum semiovale
BG = basal ganglia

Table 1.2 Effect sizes of relationship between age and DTI parameters where correlation coefficient reported

Study	<D> with age				'FA' with age		
	n	Region	Correlation	P	Region	Correlation	P
Head et al.	50	ant CC, post CC	.54 .31	<.01 NS	ant CC post CC	-.42 -.08	<.05 NS
Pfefferbaum & Sullivan	64	genu splenium cs	.5 .24 .58	<.001 <.01 <.001	genu splenium CS	-.37 -.29 -.79	<.003 <.02 <.001
Abe et al.	50	frontal lentiform thalamus other regions	.42 .44 .38 .2 to .4	.01 .02 .05 >.2	genu CC frontal, parietal, lentiform; splenium thalamus & post IC	- .54 ~ -.3 ~.1	<.001
O'Sullivan, Jones et al.	29	total D	.69	.001	Total FA	-.60	.0071
Chen et al.	54	Global Tissue	.94 .96	<.03 <.02	-		
Nusbaum et al.	20	Whole brain	.73	.0002	Whole brain	-.55	
Chun et al.	38	Whole brain	.38	<.05	-		
Virta et al.	20	peduncle pons medulla	**-ve** **-ve** **-ve**	<.0001 <.0001 .29	Peduncle (pons, medulla)		.039 (.58)

CC = corpus callosum CS = centrum semiovale

Several studies have looked at <D> (Chen, Li, & Hindmarsh, 2001; Chun, Filippi, Zimmerman, & Ulug, 2000; Helenius et al., 2002) or diffusion anisotropy (Sullivan et al., 2003; Sullivan et al., 2001; Pfefferbaum et al., 2000; Bartzokis et al., 2003; Chepuri et al., 2002) alone, but few have investigated both (Nusbaum et al., 2001; O'Sullivan et al., 2001a; Abe et al., 2002). These studies are generally fairly small, often contain a heterogeneous mixture of subjects, and although some include people into their 80s most have a mean age well below 60. As discussed below, these studies mostly concur that older subjects have a higher <D>, with correlation coefficients ranging from .1 to .9 (but see Helenius et al., 2002 and Virta, Barnett, & Pierpaoli, 1999), and lower FA with correlation coefficients from -.1 to -.6. These associations are strongest in the prefrontal cortex and anterior corpus callosum (Sullivan et al., 2001; Pfefferbaum et al., 2000; Chepuri et al., 2002).

Mean Diffusivity: Chen et al studied 54 healthy volunteers (30 male) from Stockholm aged 20-79. The mean age is not given, but 20 of the group fall in the 30-39 age group (Chen et al., 2001). They show that the ADC is higher in the older groups. The global ADC was 3% higher every decade after the age of 40, whereas the tissue ADC only increased by 1% per decade, a small absolute amount within the limit of experimental error. They hypothesise that this is due to the increase of free water with ageing (due to increasing ventricular volume, widening cortical sulci and Virchow-Robin spaces) whereas the tissue microstructure changes relatively little in normal ageing. They show no difference between ADC of white and grey matter. They also investigate technical parameters and conclude that DWI acquired by different methods are comparable as long as experimental parameters such as in-plane resolution, FOV and the degree of diffusion weighting (b) are kept constant. They advocate the use of whole brain ADC as it does not involve the bias introduced by choice of size and location of region of interest (ROI). Furthermore, as the process is automated, the operators cannot introduce bias. However, this technique will not identify true regional variations.

Age related changes in diffusion were shown by Chun et al (Chun et al., 2000) in a study of 38 American subjects (20 male) mean age 53.4 (SD 17, range 26-86 years). 11 were healthy volunteers, 27 patients, and 12 had minor abnormalities on MRI scan. ROIs were placed on <D> maps: 16-38 for periventricular white matter, and two for thalamus. <D> was found to correlate with age ($r = .38$) but the absolute increase was minimal. Increase in periventricular WM <D> correlated more strongly with age ($r = .41$) but also showed more scatter round the fitted regression line, and thalamic diffusion did not correlate with age ($r = .17$). Histological studies have shown a decrease in synaptic density in the frontal cortex after age 74 (Huttenlocher, 1979). Other putative reasons are white matter atrophy, enlarged perivascular spaces, or increased water content due to thinning of blood vessels.

One relatively large study did not find an increase in <D> with age (Helenius et al., 2002). This study scanned 80 healthy Finnish volunteers, 10 women and 10 men in each of 15-year age groups from 20 years old. There were no statistically significant

differences between the ADC of the different age groups (apart from an increase in the lateral ventricles across all ages, and an increase in ADC in the thalamus of the oldest group), between right and left hemisphere, or between the ADC of men and women. ROI were manually drawn on the T2-weighted image, in 18 neuroanatomic sites: the method of choosing the exact site and size of the ROI is not described, but the segmentation of different tissue types may account for the lack of association between age and diffusivity. The difference between this study and those presented above may also have been related to the method of analysis. MANOVA between age groups was used rather than correlation of actual age, and there may have been sufficient variation within the ten year age band to obscure any relationship. Also the group was selected to be healthy and unmedicated, and may therefore have had less intrinsic variance. As in all the studies, no account was taken of brain size or previous mental ability.

Therefore, although intuitively it would seem that <D> should increase with age, the studies published to date have not yet reached a consensus on this hypothesis. Further studies are required investigating <D> in various age groups, in particular focussing on older groups in various states of health, taking their brain size and mental ability into account. A consensus is needed on the appropriate methodology: scan parameters, ROI/whole brain analysis and statistical methodology.

Mean diffusivity and diffusion anisotropy: A Japanese study (Abe et al., 2002) of 50 healthy volunteers, mostly hospital workers or students, mean age 44.8 (SD 14, range 21-69) years used DTI to compare FA and <D>. ROI were drawn on T2-weighted images. There were no differences between hemispheres, or between men and women. The older half of the group had increased <D> in frontal white matter, lentiform nucleus and thalamus, and decreased FA in genu of the corpus callosum (and a non-significant trend to decreased FA in frontal and parietal lobes). They hypothesise that <D> changes out of proportion to FA may be due to neuronal dysfunction related to levels of synaptic proteins rather than loss of neurones or synapses. Also, they note that differences between their study and others of ageing may be due to the relatively younger age of their group. They do not consider the possibility that their selected sample may be of unusually high ability, and that this,

rather than, or in addition to age, may account for the differences between their study and others.

A research group from Stanford, California, have published the largest study of DTI and ageing to date (Pfefferbaum & Sullivan, 2003). 64 healthy volunteers (mean age 52.5 SD 20 years) had <D> and FA measured in centrum semiovale, and genu and splenium of corpus callosum. <D> increased and FA decreased with age in these areas, particularly in the centrum semiovale. This study included 49 subjects from Sullivan et al., 2001, which reported decreasing FA with age in frontal and parietal pericallosal regions, centrum, and genu of corpus callosum. The association with splenium was not significant. A previous study had also reported a negative correlation between age and FA in these regions from 31 of this group (Pfefferbaum et al., 2000). The pericallosal regions were not included in the 2003 report.

A small study of 20 volunteers from a wide age range (20-91) (Nusbaum et al., 2001) showed increasing whole brain <D> with age ($r = .73$). Relative anisotropy (RA) decreased with age in frontal, parietal and occipital periventricular white matter, genu and splenium of corpus callosum. RA was found unexpectedly to increase with age in the posterior limb of the internal capsule, and the periphery of the brain, and was attributed to probable artefact.

A study (O'Sullivan et al., 2001a) of 20 healthy elderly volunteers (age range 56-85 years) compared to ten younger volunteers (age range 23-37 years) did show increased <D> and decreased FA in the older group. DTI parameters were measured on regions of interest that contained the white matter of one whole hemisphere, divided into anterior, middle and posterior regions. There was a significant difference between the <D> of older and younger groups in all areas, and the reduction in FA in the older group was most marked for the anterior area, and was not significant in the posterior area. There was no evidence of sex differences in <D> or FA in the older group.

Virta et al. (1999) studied ten younger (mean age 29.5 years) and ten older (mean age 69.2 years) subjects and found variability in the lattice anisotropy between regions: highest in cerebral peduncle, lowest in caudal pons and intermediate in medulla. Older subjects had lower LA in the cerebral peduncle, but no differences in pons or medulla. They also found that <D> was ***lower*** in the older group in the peduncle and pons, but not medulla. They focus their discussion on the diffusion anisotropy result, and do not mention the discrepancy between their <D> result and other studies.

Diffusion Anisotropy: One study investigated whether diffusion anisotropy of the corpus callosum was related to age (Chepuri et al., 2002). 42 patients were selected from 200 undergoing brain MRI for various clinical reasons. Those selected had normal brain MRI and were over age 18 (mean age 44.2, SD 13.8 years). ROI were drawn on the areas of maximum diffusion anisotropy. The ROI varied in size, and the aniostropy index (1-volume ratio) was weighted by ROI size. They showed that anisotropy index was lowest in the genu, higher in the body and highest in the splenium. This pattern held for both sexes and all age groups, but the difference between age groups was not formally tested (and the raw data suggested that there was no consistent difference). They also examined cadaveric brains histologically, but only had a limited amount of tissue. They suggest that the orientation of the axons, and the presence of other structures could influence anisotropy. This is interpreted as showing that with ageing there is a loss of the integrity of neural microstructure e.g. myelination, microtubule and microfibre condition and integrity.

Two studies investigated diffusion anisotropy alone in the context of investigating associations with cognition (Madden et al., 2004; Stebbins et al., 2001a). Madden et al. compared 16 people mean age 64.7 with 15 mean age 20.9 and found FA decreased in all regions measured, especially the frontal region. Stebbins et al. compared 10 subjects with a mean age of 80.4 years with a matched group of 10 subjects with a mean age of 28.9 years, and found FA decreased in frontal, genu and basal ganglia, but not posterior regions.

Therefore, DTI is a useful tool to investigate normal appearing white matter with age, generally showing an increase in <D> and decrease in FA with age.

White matter lesions: White matter lesions (WML) increase with age (see Chapter 1.1.2.2). DTI may be sensitive to the ultrastructural changes which occur before WML are seen on conventional MRI. For example, one study of 60 healthy volunteers mean age 73 years (SD 5 years) (some recruited from a memory clinic but found to have no organic reason for their complaint) showed increased diffusion in WML themselves (Firbank, Minett, & O'Brien, 2003). They also found a relationship between diffusion in normal appearing white matter and white matter lesion volume. Combined with their data from magnetic resonance spectroscopy studies, these results suggest a decreased neuronal density, or reduction of myelination in the normal appearing white matter, in the presence of WML.

Several studies from a group in London have looked at patients with ischaemic leukoaraiosis (ILA) (previous lacunar stroke and diffuse white matter hyperintensities). The first examined nine patients with recurrent lacunar stroke (mean age 62 years) and ten age-matched controls (mean age 66 years) (Jones et al., 1999), and showed that <D> was increased and FA reduced in patients. There was, however, some overlap between measurements of subjects and controls. The regions of interest were both in standard areas and obviously abnormal areas. Established infarcts in three patients with carotid artery stenosis showed a marked increase in <D> and decrease in FA. It also showed that in white matter regions <D> and FA were strongly negatively correlated ($r = -.92$, $P < .0001$).

A later study (O'Sullivan et al., 2001a) assessed 30 ILA patients with mean age 69.7 (SD 8.9) years and compared them with 17 healthy controls, mean age 71.8 (SD 7.9 years). Within lesions <D> was significantly increased and FA decreased, as would be expected, but there was also a statistically significant difference between patients and controls in normal appearing white matter. This pattern was seen for both <D> and FA in the anterior periventricular region, <D> in the centrum semiovale, and no difference in the posterior periventricular region. There were also some associations

with cognitive tests (MMSE and WCST). This implies that damage to white matter tracts in ILA is not restricted to areas that are abnormal on T2-weighted MRI.

In a subsequent publication (O'Sullivan et al., 2004) this group reports results from 36 patients with ILA (mean age 69.5, SD 8.8, range 50-84) and 19 controls (mean age 71.6 SD 7.5 range 56-84). It is not clear if any subjects contributed to both studies. ROI for this study were 3x3 voxels placed on the T2-weighted image in anterior and posterior periventricular regions, and centrum semiovale. Comparing lesions to controls, D was significantly higher and FA significantly lower. However, when normal appearing white matter was compared to controls, this pattern was seen only in the anterior periventricular region.

One small longitudinal study compared scans taken a mean of 20 (SD 4) months apart in ten patients with leukoaraiosis (mean age 73 years). They found no change in the WML burden assessed by the Fazekas scale (Fazekas et al., 1987) but the brain volume decreased and <D> measured over the whole brain increased (Mascalchi et al., 2002). They therefore suggest that a whole brain <D> may be more sensitive than conventional scoring systems for monitoring subclinical progression of leukoaraiosis.

In summary, there is evidence that the presence of WML influences DTI parameters, both within the lesions themselves, and elsewhere in the brain. The changes are not, however, uniform throughout the brain, so it is important both to account for WML in analyses and to carefully consider what method is most appropriate for making measurements of diffusion parameters.

1.1.3.2 DTI and cognitive ageing

Although several studies have examined DTI changes with normal ageing, and many have focussed on disease states that increase with age e.g. cerebrovascular disease, dementia or Parkinson's disease, few have directly examined DTI changes with normal cognitive ageing.

Only three published studies (including our own (Madden et al., 2004; Shenkin et al., 2003; Stebbins et al., 2001b) were identified examining DTI and normal cognitive ageing (Table 1.3). Results from the study reported only in abstract form to date (Stebbins et al., 2001a) are reported in two review papers (Moseley et al., 2002; Sullivan et al., 2003). In general, as will be shown below, these studies are underpowered and use varying methodology, but there is most evidence for a relationship between DTI parameters in frontal regions and executive dysfunction.

Table 1.3: Studies of DTI parameters and cognitive ageing

Study	n Old	Young	Age Old	Young	Recruited from	ROI	Regions	Cognitive tests	D correlates	Effect size	FA correlates	Effect size
Madden et al. (2004) Durham, NC, USA	16 50% men	15 43-50% men	60-70 Mean 64.7	19-25 Mean 20.9	Community	Manual on tensor image	- CC: genu & splenium - AL IC - frontal - posterior	Choice response time	-	-	ALIC with RT	r = -.55
Shenkin et al. (2003) Edinburgh, UK	28	none	80 Mean 79.8 SD .4	-	Community	Semi-automated on structural image	- frontal - occipital - CS	MHT age 11 & 80, NART, MMSE, VF	CS with MMSE	ρ~ -.4	CS with - MHT11 - MHT80 - NART Frontal with MHT80	ρ .4 to .5
O'Sullivan, Jones et al. (2001) London, UK	17 76.5% men	Did not do cog tests	56-85 Mean 72 SD 8	-	Research Unit and GPs	Semi-automated on FA	WM of one hemisphere: - anterior - middle - posterior	WCST, RTMT, VF, MMSE, NART-R	Frontal with RTM Middle with RTM	r~.5	Middle with VF	r~.6
Stebbins et al. (2001) abstract Chicago / Stanford, USA	10	10	Mean 80.4 SD 5.7	Mean 28.9 SD 3.5 Matched	Healthy, highly educated	NR	? - CC - frontal - posterior - BG	RT, SDMT, RPMT, premorbid IQ	-	-	Frontal with SDMT, RT	r =.8 to .9

WCST = Wisconsin Card Sorting Test
VF = Verbal Fluency: test of executive function
NART-R = National Adult Reading Test-Revised: test of prior IQ
MHT = Moray House Test : test of verbal reasoning
SDMT = Symbol Digit Modalities Tests: test of processing speed
RSPM = Ravens Standard Progressive Matrices Test: test of non-verbal reasoning
RTM = Reitan Trail Making Test B-A (high score = worse): test of attentional set-shifting and executive function
RT= reaction time

CC = corpus callosum
ALIC = anterior limb internal capsule
CS = centrum semiovale
BG = basal ganglia
NR = not reported

The cortical disconnection theory in the context of DTI was introduced by O'Sullivan et al., 2001. This study compared DTI parameters in older and younger people, and seventeen people from the older group (mean age 72) underwent neuropsychological tests. There were significant correlations between (1) <D> of anterior regions and performance on Reitan Trail Making B-A (a test of attentional set shifting and executive function) ($r = .61$; $P < .05$) and (2) FA of middle regions and Verbal Fluency ($r = .61$; $P < .05$). These results were independent of age, sex, white matter volume, MMSE and premorbid IQ assessed by NART. Although the study was not powered to investigate structural-functional associations, and these correlations could be Type I errors (they have large confidence intervals owing to the small number of subjects), they are consistent with loss of white matter structure leading to the "disconnection" of cortical areas and the disruption of large-scale neurocognitive networks.

Results of a study published to date only in abstract form (Stebbins et al., 2001a; Stebbins et al., 2001a) are reported in Moseley et al., 2002. This study compared ten healthy subjects with mean age 80.4, SD 5.7 years with ten subjects mean age 28.9, SD 3.5 years. They show FA decreased in the older group, particularly in the frontal white matter, genu and basal ganglia outflow. They also report a correlation between frontal FA and performance on Raven's matrices (RSPM), reaction time and Symbol Digit Modalities Test (a test of speed of processing), but not MMSE, pre-morbid IQ or education. The lack of detail in the report means that it is not clear whether this is in the whole group, or just the older group, and issues such as WML are not discussed.

Results from a subgroup of 28 people from the Simpson's study have been published (Shenkin et al., 2001), and this was the largest study of DTI and cognitive ability to date, with the narrowest age range (mean age 79.8, SD 0.4 years). These subjects were all born in 1921, and sat the MHT aged 11. We found an association between <D> in centrum semiovale and global ability assessed by MMSE ($\rho = -.41$, $P = .03$), and FA in frontal regions and centrum semiovale and verbal reasoning (MHT frontal $r = .51$, $P = .01$; centrum $r = .41$, $P = .03$). Intriguingly there was an association

between centrum FA and measures of childhood IQ estimated in older age using NART ($r = .46$, $P = .01$), and measured at age 11 using the MHT ($r = .42$, $P = .03$). It is therefore possible that associations seen in older age between DTI parameters and cognitive ability may be due to a life-long association between white matter tract integrity and function rather than a late-life change. It is important to consider early life ability in studies of cognitive ageing.

Although not directly reporting psychometric tests, two other relevant studies are described here. Firstly, Madden et al. (2004) measured response time (RT) in a visual target detection task for sixteen people in each of older (mean age 64.7 years) and younger (mean age 20.9 years) groups. Subjects were presented with a standard (square), target (circle) or novel (photograph of an everyday object), and had to press the same button for standards (87% of trials) and novels (6%), but a different button for targets (7%). This task therefore has an attentional component and perceptual-motor demands. Response time was higher in the older group. Correlations are not presented for all the regions with RT, but instead analysed as contributing (or not) to a stepwise regression analysis with RT as dependent variable. Only age, FA of anterior limb of internal capsule, and splenium contributed to the model. RT correlated with FA in the anterior limb of internal capsule $r = -.55$, $P < .05$ for the older group, and with splenium $r = -.54$, $P < .05$ for the younger group, suggesting that older adults' performance in this task is influenced more by the integrity of the white matter circuits connecting the prefrontal cortex and subcortical structures than the integrity of circuits within the prefrontal cortex itself.

Secondly, the studies reported above by Sullivan and Pfefferbaum (Sullivan et al., 2001; Sullivan et al., 2001) showing a decrease in FA with age also showed a correlation between FA and neuromotor tasks. Only 19 of the subjects took the neuromotor tests (standard tests of gait and balance, and a test of tapping a key with forefingers separately then alternately). One-foot standing correlated with FA in genu, splenium, centrum, parietal pericallosal regions (r .5 to .6), but not frontal regions. Scores on a finger-tapping test (of inter-hemispheric transfer) correlated with FA in splenium ($r = .56$, $P < .02$) and parietal pericallosal regions ($r = .61$, P

<.008) better than did age. This suggests that regional white matter coherence is important for gait, balance and tests of interhemispheric transfer.

Specific disease states such as Alzheimer's disease can provide further clues as to the relationship between DTI and cognition. One study (Bozzali et al., 2002) of 16 patients (mean age 69.6 years) and ten controls (mean age 66.1 years) showed a strong correlation between MMSE score of patients and <D> (r = -.92) and FA (r = .78). <D> was higher and FA lower in the patients in corpus callosum, frontal, temporal and parietal lobes, but not other areas. The selective involvement of the association cortices suggests that Wallerian degeneration of white matter fibre tracts secondary to neuronal loss in the associative cortex contributes to the pathogenesis of Alzheimer's disease. These imaging results have been corroborated by a study comparing post-mortem MRI and histopathology of six brains of patients with Alzheimer's disease (Bronge, Bogdanovic, & Wahlund, 2002). They found that abnormal regions on the pathology specimens were greater than the white matter changes seen on scans (by 50%). The abnormal regions not identified in the MRI scan, however, showed only minor changes: lower intensity of myelin staining, accentuation of the distance between fibres, but preserved axonal network and glial cell density. It therefore seems likely that DTI may be sensitive to subtle changes in brain structure which occur with ageing.

This literature review has introduced the concept of DTI as a useful technique for ultrastructural changes in the brain, particularly in white matter. Structural MRI scans describe an increase in white matter lesions (WML) with age, and show a weak association between WML and cognitive tests, particularly executive function (Chapter 1.1.2.2). <D> increases and FA decreases both within WML and in surrounding normal-appearing white matter. It is therefore important that DTI studies include some assessment of WML in the analysis.

The majority of DTI studies published to date are small and vary in methodology, making general conclusions difficult. The majority of evidence points towards an increase in <D> and decrease in FA with age. There is less evidence for the

relationship between DTI and cognition, but a suggestion of increased <D> and decreased FA correlating with worse cognitive function, perhaps most strongly in frontal regions and for tests of executive function.

In this thesis measures of brain size, WML and white matter integrity (DTI) are correlated with cognitive ability in a cohort of relatively healthy older people.

1.2 Developmental origins of adult health and disease

In the past 50 years, adult chronic disease has become the main public health problem of industrialised countries: by 2000 non-communicable diseases accounted for 83 – 89% of deaths in the developing world, with 50% due to cardiovascular disease, cancers, chronic obstructive lung disease and diabetes (World Health Organisation, 2000). Traditionally, the aetiological models focussed on adult risk factors such as cigarette smoking, obesity and cholesterol, and preventive strategies encouraged healthier lifestyles. However, these strategies did not have a major impact, and researchers began to consider whether influences from earlier life might be important in determining chronic disease (Barker, 1994; Langley-Evans, 2004; Kuh & Ben-Shlomo, 1997). Ecological studies in the north of England showed a strong correlation between infant mortality (and thus prenatal or early life deprivation) and adult mortality from coronary heart disease, stroke, obstructive lung disease and lung cancer (Barker, 1994).

This led to an explosion of research using birth weight as a marker of prenatal influences on adult chronic disease. There is most evidence to support an association between birth weight and cardiovascular disease and type II diabetes (Barker, 2004), but associations have been reported for birth weight and many different diseases, such as cerebrovascular disease, hypertension, respiratory and allergic disease, osteoporosis and some cancers (Kuh et al., 2003). The importance of early life for the development of later disease was initially termed the Fetal Origins (or Barker) hypothesis, and defined as:

> "that cardiovascular disease and type 2 diabetes originate through developmental plasticity, in response to undernutrition…Plasticity is …the ability of a single genotype to produce more than one alternative form of

> structure, physiological state or behaviour in response to environmental conditions." (Barker, 2004 p. 114)

Since it is now established that growth during infancy and early childhood, in addition to fetal life, is linked to later disease, the term *Developmental Origins of Adult Health and Disease* is now preferred (Barker, 2004).

The idea of critical or sensitive periods in early life having lifetime consequences ("programming") was well-established in developmental biology before Barker's work. For example, in 1873, the critical period for imprinting in birds was described (Lucas et al., 1999). Forsdahl, in 1967, described increased adult cardiovascular mortality where infant mortality was highest (Forsdahl, 1967; Langley-Evans, 2004), and Dubos in 1966 (reprinted in Dubos, Savage, & Schaedler, 2005) noted that "early experiences…affect profoundly and lastingly many biological characteristics of the adult." (p. 5).

Various theories have been advanced as to the reason for an association between low birth weight and later disease. The realisation that the highest risk of the metabolic syndrome was for babies who had low birth weight but then increased their weight rapidly in early life, led to the concept of the 'thrifty phenotype'. This suggested that an adverse fetal environment programmed the fetus to expect an adverse postnatal environment. As the adaptations in response to the prenatal stresses were irreversible, the newborn child would be best suited to a deprived postnatal environment, and if faced with excess nutrition rather than deprivation it would have an increased risk of disease (Barker, 2000). The term 'predictive adaptive response' is used to describe responses made by the developing organism, not for immediate advantage, but for adaptive advantage in the environment it predicts it will face in adulthood. Later disease risk is suggested to be dependent on the degree of mismatch between the environment predicted prenatally and that actually encountered in later life: the greater the mismatch the greater the risk of disease (Gluckman, Hanson, Morton, & Pinal, 2005).

Research on the Developmental Origins of Health and Disease initially concentrated on the dichotomous outcome of the presence or absence of disease, such as cardiovascular disease (both morbidity and mortality), but then extended to include continuous variables such as blood pressure or cholesterol. This used actual continuous measurements rather than categorising them arbitrarily into 'hypertensive' or 'normal'. The move from dichotomous to continuous variables has allowed a shift in focus from disease to variations in outcome measures in health – "individual differences". One such example is cognitive ability, and the evidence for developmental influences on cognitive ability in the normal range in adults is reviewed below. Developmental origins for cerebrovascular disease are then considered. Finally, the concept of a *life course approach* is discussed: that experiences at different stages in life (from pre-conception to old age) influence later health and disease, and that genetic factors are also important.

1.2.1 Developmental origins of cognitive ability

Interest in whether prenatal influences affect cognitive abilities predates the recent resurgence of interest in the Developmental Origins of Health and Disease (Jackson, 1996). Premature and low birth weight (<2,500g) babies perform less well than their term or normal birth weight peers (Bhutta, Cleves, Casey, Cradock, & Anand, 2002; Corbett & Drewett, 2004), with heavier babies tending to perform better. Six studies of cognitive outcomes of term babies within the normal birth weight range (>2,500g) have shown that there is a small, consistent, positive association between birth weight and childhood cognitive ability, even when corrected for confounders (Record, McKeown, & Edwards, 1969; Matte, Bresnahan, Begg, & Susser, 2001; Shenkin et al., 2001; Richards, Hardy, Kuh, & Wadsworth, 2002; Jefferis, Power, & Hertzman, 2002; Corbett, Durham, Wright, Tymms, & Drewett, 2005). The effect size is small, typically around 1% of the variance (Shenkin, Starr, & Deary, 2004). A major concern when relating birth weight to later outcomes is the importance of social class: this could be a confounder in any relationship, or alternatively be the mechanism which explains a relationship. In the studies reported above, parental social class accounts for a larger proportion of the variance than birth weight, and these two variables are largely independent. For a systematic review of this literature, see Shenkin et al., 2004.

This thesis is concerned with the influence of birth weight on cognitive ability in adult life. Five studies include data from beyond childhood (age 16). Two studies assessed participants at army recruitment; (Sorensen et al., 1997; Seidman et al., 1992) one childhood cohort study followed participants to age 43 (Richards et al., 2002); and one retrospective cohort study recruited participants with a mean age of 60.9 years (Martyn, Gale, Sayer, & Fall, 1996). A further retrospective cohort study (Gale et al., 2003) studied subjects with a mean age of 69.8, but the primary data reported in the paper relate to head size rather than body size. These studies are reviewed below in chronological order of reporting, and summarised in Table 1.3, Table 1.4 and Figure 1.3

Table 1.3: Studies of birth weight and adult cognitive ability (age at testing > 17 years)

Study	Source	Birth Year	Birth n	% male	Test Year	Test n	% male	Test Age	Test	Validation
Seidman et al. 1992 Retrospective matching of data	Maternity ward births in W. Jerusalem, at Israel Defence Forces Draft	1964- 1970	NR "<2% excluded"	NR	NR probably 1981-87	20,567	100	17	Translated Verbal Otis test and non-verbal matrices	"transformed into values that correlate with WAIS"
Sorensen et al. 1997 Retrospective matching of data	Births in Denmark, registered with draft board 5th conscription district	1/1/1973- ?	NR BW measured in 250 g categories	NR	1/8/1993-31/7/1994	4,300 matched to birth data	100	"about 18"	Boerge Prien test (max 78)	correlates .82 with full scale IQ on WAIS
Martyn et al. 1996 Retrospective matching of birth data, & cross-sectional data collection	Singletons born in two hospitals in Preston & Sheffield, UK still living in area	1920-1943	NR	NR	NR	1,576	NR	mean 60.9 (SD 2.1) differs by area	AH4 Mill Hill	NR
Richards et al. 2002 Prospective data collection	MRC national survey of health and development (NSHD). Singletons UK	One week in March 1946	(5,362) 3,900 complete data	NR	(1954 1961 1972) 1989	2,136	NR	(8,15, 26) 48	Verbal memory (15 item word list learning)	no (devised by NSHD) (age 8 -26 tests referenced)
Gale et al. 2003 Retrospective matching of birth data, & cross-sectional data collection	Babies born in one hospital in Sheffield, UK, still living in area	1922-1930	4,793	NR	2000-2001	215	54	mean 69.8 (SD 2.0)	AH4 Weschler logical memory	referenced

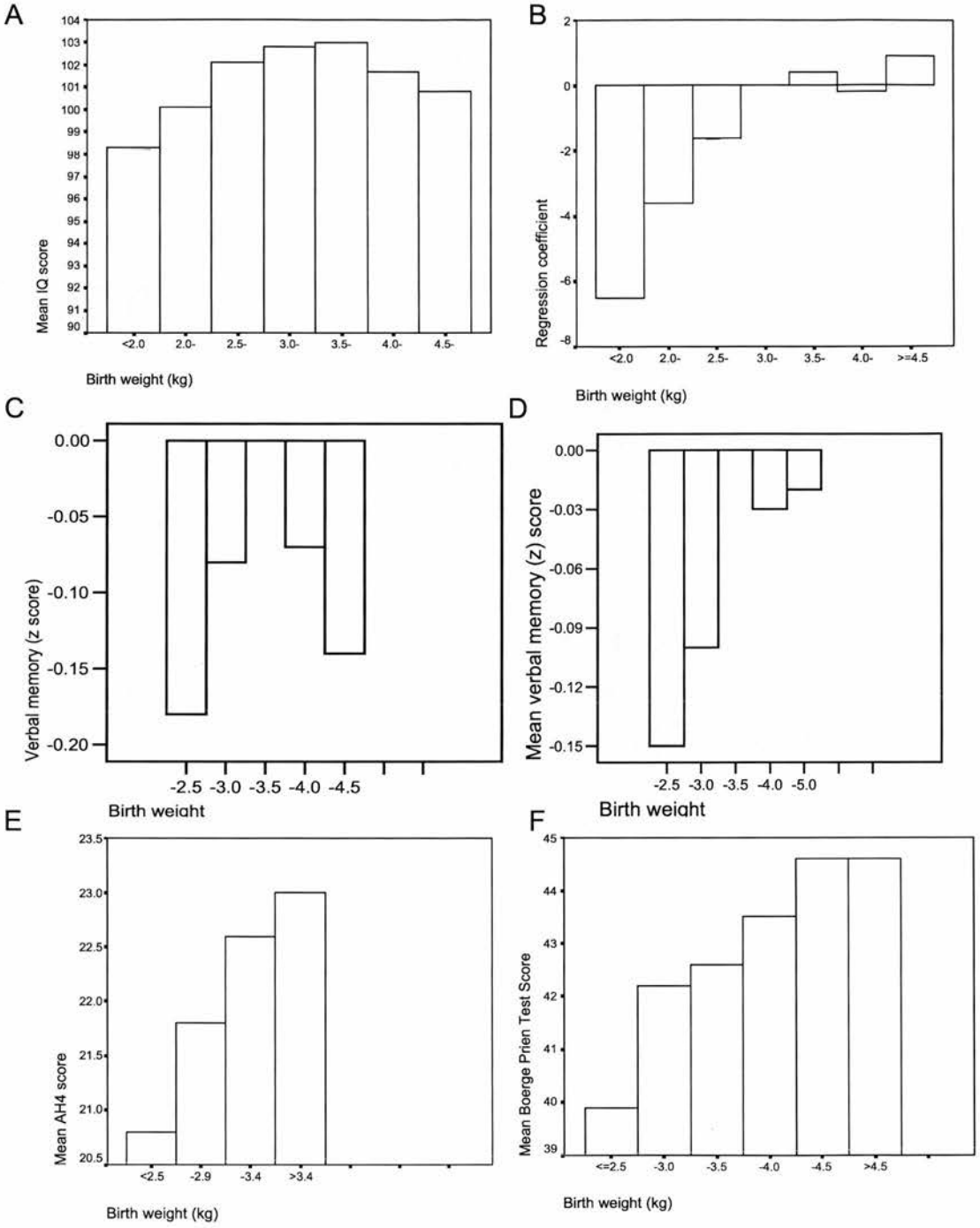
BW = birth weight NR = not reported NSHD = National Survey of Health and Development

Table 1.4: Results of studies of birth weight and adult cognitive ability

Study	Categorical data uncorrected				Correlation uncorrected	Correlation corrected for confounders	Confounders considered	IQ test blind to BW?	Notes
	BW (kg)	IQ mean	SD	n					
Seidman et al.	<2.0 2.0- 2.5- 3.0- 3.5- 4.0- 4.5-	98.3 100.1 102.1 102.8 103.0 101.7 100.8	14.9 15.9 17.3 18.5 15.3 16.0 15.8	224 704 3342 8555 5896 1595 251	NR	β (SE) -6.5 (1.1) P <.0001 -3.6 (.6) P <.0001 -1.6 (.3) P <.0001 reference group .4 (.3) P = .16 -.2 (.4) P = .72 .9 (1.0) P = .37	BR MA ethnic origin (paternal birth county) SC (residence & tax level) PE	Y (NR)	Bar chart shows IQ scores of LBW compared to NBW normal distribution shifted to left. Confounders explain 22% of variance.
Sorensen et al.	-2.5 -3.0 -3.5 -4.0 -4.5 >4.5	39.9 42.2 42.6 43.5 44.6 44.6	9.3 9.3 9.7 9.4 9.6 9.5	171 603 1451 1453 515 105	NR	Graph of quadratic spline regression : non-linear relationship	GA BR MA Marital status Employment Birth length	Y (NR)	
Martyn et al.	<2.5 -2.9 -3.4 >3.4	20.8 21.8 22.6 23.0	NR	74 266 543 693	NR	NR P = .17	age SC individual dataset	NR	Also assessed decline in cognitive function P = .42
Richards et al.	 -2.5 -3.0 -3.5 -4.0 -5.0	*z* score - .18 - .08 ref -.07 -.14	95% CI -.39 to -.04 -.21 to .-05 ref -.17 to -.03 -.29 to -.01		P = .23	kg *z* score (95% CI) -2.5 -.15 (-.36 to -.05) -3.0 -.10 (-.22 to -.02) -3.5 reference -4.0 -.03 (-.13 to -.07) -5.0 -.02 (-.17 to -.12) P <.36	sex BR MA SC (father's occupation) PE (maternal) (postnatal height and weight)	NR	followed longitudinally age 8 -43
Gale et al.						b = .634 (-1.33 to 2.6) P = .525	none	NR	Study mainly considers head size

BW = birth weight GA = gestational age PE = parental education BR = birth rank MA = maternal age
IQ= cognitive test score SC = social class
NR = not reported Y = yes

Figure 1.3: Birth weight and mean cognitive test scores in adulthood



A Seidman. (1992) Israel; n = 20,567
B Seidman corrected for ethnic origin, birth order, maternal age, parental education, social class
C Richards. (2002) UK; n = 2,136
D Richards. corrected for sex, birth order, social class, maternal education, maternal age
E Martyn (1996) UK; n = 1,576
F Sorensen. (1997) Denmark; n = 4,300

Jerusalem Perinatal Study (Seidman et al., 1992)

The first study (Seidman et al., 1992) retrospectively matched the data for 20,567 children who were born in a maternity ward in West Jerusalem, Israel, between 1964 and 1970 and who were drafted to the Israeli army at age 17 (exact age is not reported). The analysis is restricted to males only. Intelligence test scores (uncorrected for potential confounders) increased with increasing birth weight (from mean IQ of 98.3 (SD 14.9) for weights <2,000g to 103.0 (SD 15.3) at 3,500 – 4,000g), but decreased beyond 4,000g to 100.8 (SD 15.8) for weights > 4,500g (Table 1.4; Figure 1.3). Confounders examined were social class (municipal tax level and area of residence, not paternal occupation), ethnic origin, maternal age, parental years of education and birth order. They do not include, most importantly, gestational age, or marital status, education or any post-natal factors. There is no mention as to whether multiple births were excluded. When corrected for confounders regression coefficients show an increase in IQ for birth weight, particularly in the lower birth weight categories (i.e. up to 3,000 – 3,500 g), (regression coefficient -6.5 IQ points (SE 1.1) for < 2,000 g; -3.6 (SE .6) for 2,000 – 2,499g) and the decrease at the higher values is no longer evident (Figure 1.3 A and F). Multiple regression showed that birth weight, ethnic origin, paternal education, maternal age, birth order and social class together explained 22% of the variance in intelligence test scores. The authors acknowledge the risk of selection bias due to the lack of gestational age (e.g. all those missing could be preterm). The restriction of the sample to males only limits its generalisability. However, this study indicates that birth weight and social factors both have an influence on cognitive ability into adolescence in this sample.

Danish Conscripts Study (Sorensen et al., 1997)

The second study conducted at army recruitment is from Denmark, of boys born from 1973 drafted at the age of 18 (again the exact age is not reported) (Sorensen et al., 1997). Of 5,183 men drafted, 4,661 underwent a medical examination (remainder excluded due to illness), and of these 92.2% (n = 4,300) were matched to their birth details. Whether this introduces any selection bias is not discussed, nor is whether multiple births are excluded. The test used, the Boerge Prien test, is reported as correlating highly with the WAIS. Score on the Boerge Prien test increases with

increasing birth weight (from mean score of 39.9 (SD 9.3) out of 78 at < 2,500g to 44.6 (SD 9.5) at > 4,500 g) (Table 1.2), flattening at > 4,500 g (Figure 1.3). When corrected for the confounders of gestational age, birth length, maternal age, parity, marital status and employment (employed, unemployed or self employed) the mean score increases with birth weight from 1,900 to 4,200g (data not shown here, illustrated graphically in the paper). There is some reduction in test score at the highest weights, suggested to be due to underlying disease or birth trauma. The social descriptors are very crude and there may be important differences within employed groups that will not be recognised here. Other potential confounders that were not assessed include parental IQ and postnatal factors, and once again the results are restricted to males.

Preston and Sheffield, U.K., study (Martyn, Gale, Sayer, & Fall, 1996)

The smallest of these studies following participants into adulthood has the oldest subjects (Martyn et al., 1996). It includes both male and female singleton children, but has a large potential for selection bias. Of those invited to take part in the study 1,576 (47.5%) agreed, with very different uptake rates from different areas. The overall mean age was 60.9 years (SD 2.1), but in one area the mean was 52.1 (SD .6), and in another 68.6 (SD 1.4). Participants took part one of the Alice Heim 4 test, estimating fluid intelligence, and the Mill Hill vocabulary test, which estimates crystallised intelligence. Birth weight is reported in pounds, from < 5.5 lb to > 7.5 lb, equivalent to < 2,500 to > 3,400 g, therefore the range is restricted at the top end compare to most of the other studies. Mean AH4 score increases with increasing birth weight (from 20.8 (SD not reported) at < 2,500g to 23.0 at > 3,400g) (Table 1.4, Figure 1.3D), but does not reach statistical significance. This association is not reported corrected for confounders, although it is reported that similar results were achieved when excluding subjects born before 38 weeks. There was an association between biparietal diameter of the head at birth and AH4 score (P = .008) which persisted when corrected for age, social class and individual dataset (i.e., place of birth and current residence) with score increasing by 3.7 for every 2.5 cm increase in diameter. This may be a type I error, in light of the multiple correlations performed,

but raises the possibility of the use of other measurements at birth which may reflect insults to growth at different stages in prenatal development.

A subsequent publication by the same research team on a different cohort (Gale et al., 2003) focuses on the relationship between head size and cognitive function in 215 subjects born in Sheffield between 1922 and 1930. This study also examines the association between birth weight and AH4 score at mean age 69.8 years (SD 2.0), and found no association between birth weight and score on AH4 in older age. It did, however, find an association between adult head size and test score, suggesting the importance of postnatal brain and head growth (see below).

British 1946 birth cohort (Richards et al., 2002)

The 1946 birth cohort (Richards, Hardy, Kuh, & Wadsworth, 2001) prospectively followed a representative sample of all single and legitimate births in England, Scotland and Wales in one week in March 1946. Participants have been tested cognitively at age 8, 15, 26 and 43 to date. Cognitive function increased with increasing birth weight up to the highest birth weight category at age eight, and although the association persisted into adulthood, the effect of birth weight on test scores at age 11, 15, and 26 was largely accounted for by its effect at age eight. At age 43, when up to 68% of those who participated at age eight were still involved, birth weight had no significant effect on test scores (verbal memory, search accuracy or search speed) (Table 1.4, Figure 1.3 C). However, once confounders are included in the analysis there appears to be a relationship between birth weight <3.0kg and verbal memory score. This does not reach conventional statistical significance. The absence of an association between birth weight and cognitive ability age 43 may be artefactual due to the shift from psychometric tests of general ability to memory tests, due to the influence of the trait of intelligence from earlier life, or could be due the increasing influence of adult environmental influences or genetics.

Head size Head circumference at birth is an indicator of brain growth during fetal life, whereas adult head circumference reflects brain growth in the first few postnatal years, reaching 93% of its final size by age six (Gale et al., 2003). Therefore an

association between head/brain size (rather than body size) and cognitive ability would support the "brain sparing hypothesis", that in the face of inadequate supply nutrients are diverted to the brain at the expense of the trunk (Barker, 2004). Martyn et al (1996) found an association between biparietal diameter and cognitive function (AH4) in 581 subjects aged 48 to 74 years. There was no association with head circumference or occipitofrontal diameter, and therefore this may merely be due to chance. This study has a significant loss to follow-up which may bias the results (but only if relations between birth measurements and cognitive function are different in responders and non-responders). Gale et al (2003) studied 215 people mean age 69.8 years (SD 2.0). They found no association between head circumference at birth and cognitive ability (AH4, Wechsler Logical Memory test). However there was a statistically significant association between *adult* head circumference and AH4 score. The authors conclude, from this study and a subsequent one with head size measured prospectively from prenatally from 18 weeks gestation to 9 years (Gale, O'Callaghan, Godfrey, Law, & Martyn, 2004) that postnatal brain growth is more important than prenatal for cognitive ability. Few studies, however, include measures of body proportions such as head size.

In view of the conflicting evidence as to whether there is a relationship between birth weight and cognitive ability in old age, the scarcity of studies beyond age 60 and absence of studies beyond age 80, we investigated the relationship between birth weight (and other early life parameters) and cognitive ability in old age (75 to 80 years).

1.2.2 Developmental origins of cerebrovascular disease and vascular risk factors

As discussed above (Chapter 1.1.2.2) cerebrovascular disease can result in the clinical endpoint of stroke, or more subtle changes such as WML or loss of white matter integrity (cortical disconnection). Studies of early life influences on cerebrovascular disease which have considered stroke morbidity and mortality will be reviewed below, but there is a need for studies with more sensitive outcomes.

There is substantial evidence from cohort studies that increasing birth weight is associated with a decreased incidence of cardiovascular disease, with approximately a 20% reduction in risk of cardiovascular disease per kilogram increase in birth weight (Rich-Edwards, 2004). The evidence for cerebrovascular disease is less consistent. Studies investigating this have mostly examined stroke in addition to coronary heart disease as an outcome. Martyn et al. (Martyn, 1996) studied 13,249 men in Hertfordshire and Sheffield, and found a 28% decrease in stroke mortality per kg increase in birth weight ($P < .05$). Leon (1998) (Leon et al., 1998) found a 29% decrease in overall stroke mortality for men and 16% for women per kilogram increase in birth weight from 14,611 Swedish births ($P > .05$). In this cohort, incidence of occlusive stroke decreased by 7% (-9% to 20%, $P = .29$) per kilogram birth weight, and haemorrhagic stroke by 41% (17 to 57%, $P = .009$) per kg (Hypponen, Leon, Kenward, & Lithell, 2001). Eriksson (2000) (Eriksson, Forsen, Tuomilehto, Osmond, & Barker, 2000) studied 3,639 Finnish men and found an 18% decrease in stroke events per kg ($P = .03$). The largest epidemiological study of 70,297 female US nurses (Rich-Edwards et al., 1997) found a 15% decrease in stroke events per kg ($P = .004$). A subsequent study of 66,111 of this group found a hazard ratio of .84 (95 % confidence interval .76 to .93) for total stroke, .83 (.71 to .96) for ischaemic stroke and .86 (.66 to 1.11) for haemorrhagic stroke (Rich-Edwards et al., 2005).

These studies have variously been criticised for loss to follow-up, use of self-reported birth weight, use of either fatal or non-fatal end points, failure to adjust for socio-economic status or lifestyle risk factors (Kramer, Seguin, Lydon, & Goulet, 2000; Rich-Edwards, 2004). However, individual studies within this group have dealt with these criticisms. For example, Leon et al. (1998) had almost complete follow-up of their birth cohort by using national personal identity numbers; only the American Nurses' Study relied on recall of birth weight (Rich-Edwards et al., 2005), with the others using original records; socioeconomic status at different points in life was collected in the UK, Swedish and Finnish studies (Martyn, 1996; Eriksson et al., 2000; Hypponen et al., 2001), and the US and Swedish studies collected data on adult lifestyle factors such as smoking, diet and family history (Rich-Edwards, 2004;

Rich-Edwards et al., 1997; Leon et al., 1998). There collectively appears to be a robust association between birth weight and stroke which may be stronger for haemorrhagic stroke (Hypponen et al., 2001; Rich-Edwards, 2004) (but see Rich-Edwards et al., 2005 which found almost the same hazard ratio for occlusive or haemrrhagic stroke, with wider CI for haemorrhagic stroke).

Neuroimaging can distinguish ischaemic from haemorrhagic stroke (although reliability depends on time from infarct, and whether CT or MRI is used), but no studies were identified which used neuroimaging as an outcome in studies of early life influences on cerebrovascular outcomes.

The relationship between birth weight and stroke may be due to (mediated by) a relationship between birth weight and cardiovascular risk factors (e.g. blood pressure, cholesterol, diabetes). For example, a meta-analysis of studies of birth weight and blood pressure found that blood pressure decreased by 1-2 mmHg per kilogram increase in birth weight, with the effect increasing with age (Huxley, Shiell, & Law, 2000). This association may, however, have been due to small study size, inadequate control for confounders, inappropriate adjustment for current body weight and publication bias (Huxley, 2004). Some studies have suggested a relationship between birth weight and cholesterol metabolism, with a meta-analysis (Owen, Whincup, Odoki, Gilg, & Cook, 2003) finding a decrease in cholesterol of 0.05 mmol/l per kilogram increase in birth weight. However, given the high correlation between birth weight and other birth measures such as abdominal circumference which reflects hepatic development, there was little evidence to suggest a specific effect of birth weight on cholesterol. The risk of type II diabetes decreased twofold from the lowest to highest birth weights (Rich-Edwards et al., 1997). Studies that adjust for cardiovascular risk factors find that these factors do not explain the association of birth weight with cardiovascular disease (Koupilova, Leon, McKeigue, & Lithell, 1999; Rich-Edwards, 2004; Rich-Edwards et al., 1997), but it is important to consider whether early life influences on cardiovascular or cerebrovascular disease act via particular risk factors.

Cardiovascular risk factors (blood pressure, cholesterol, impaired glucose tolerance) all result in the common endpoint of atheroma, which can be detected non-invasively, accurately and reliably in the lower limb using the ankle-brachial pressure index (ABPI) (Fowkes, 1991; Fowkes, 1988), and in extracranial carotid arteries using duplex ultrasonography (proportion of the lumen occluded, or intima-media thickness (IMT)) (Grobbee et al., 1994). ABPI, carotid artery stenosis and CIMT have all been associated with cerebrovascular events and WML on MRI scans (Bots et al., 1997; Bots et al., 1993), and carotid atheroma has been associated with cognitive impairment (Auperin et al., 1996; Mathiesen et al., 2004).

One study has investigated the relationship between birth weight and ABPI in 186 subjects in Sheffield, mean age 68 years (Martyn, Gale, Jespersen, & Sherriff, 1998), finding no significant association (P for trend .36). However, mean birth weight was lowest in people with the lowest ABPI (odds ratio 2.3 (95% CI 1.0 to 5.6), 115 oz (SD 21) for ABPI < 1.05, 118 (SD 18) for ABPI >1.24, P for trend .36). There was no association between ABPI and other birth parameters (length, abdominal circumference, placental weight), but a non-significant trend towards lower ABPI with smaller head circumference.

In the Sheffield cohort (Martyn et al., 1998) there was an association between birth weight and carotid stenosis, with the prevalence and severity of carotid atherosclerosis greatest in those with the lowest birth weight (OR for weight <= 6.5 lb compared to >7.5lb = 5.3 (95% CI 2.0 to 14.0, P .003). This association remained significant after adjustment for hypertension, systolic blood pressure, cholesterol, smoking status and gestational age. Several studies have investigated the relationship between birth weight and carotid atherosclerosis using an average of IMT measured over 6 sites in common and internal carotid arteries. These include a wide range of ages from early adulthood to older age. Oren et al (Oren et al., 2004) examined 750 Dutch men and women aged 28 and found no overall relationship between IMT and birth weight. However, those with low birth weight who showed exaggerated postnatal growth had a significant association with IMT. Lamont et al (Lamont et al., 2000) studied 347 people aged around 50 in the "Newcastle thousand families" birth

cohort and found a small but significant relationship between birth weight and IMT in men (standardised beta -.17 [95% CI -.33 to -.02] per SD) but not women (beta -.04 [-.18 to .10]). Adult lifestyle (physical activity, diet, and smoking) and biological risk markers (e.g. waist to hip ratio, blood pressure, lipids) were more important determinants of cardiovascular health than early life factors. The largest study to date based on the ARIC study in the US studied 9,581 subjects aged 45 – 64 years (Tilling et al., 2004). Univariate analysis found a *positive* relationship between (recalled) birth weight and IMT, accounting for less than 1% of the variance in IMT. This becomes non-significant when corrected for confounding factors. The finding of a positive relationship has led to the suggestion that early life influences may have a role in the transition from atherosclerosis to atherothrombosis, rather than being associated with atherosclerosis formation *per se*. A second study in Sheffield included older subjects (Gale, Ashurst, Hall, MacCallum, & Martyn, 2002) with 389 participants mean age 70.0 years. There was a non-significant trend to increased risk of carotid stenosis >30% in smaller birth weights (OR < 6.5 lb 1.8 [95% CI 1.0 to 3.3]). IMT showed a sex difference, with women showing an inverse relationship between birth weight and IMT (non-significant once corrected for vascular risk factors and gestational age) whereas men showed a *positive* relationship (i.e. increasing birth weight associated with increasing carotid atheroma). This finding was unexpected and may have been due to chance.

In view of these conflicting results there is a need for further studies of the influence of early life factors, including birth weight, on cerebrovascular disease and associated risk factors: "[w]hether increased atherogenesis is indeed one of the mechanisms underlying the link between poor fetal growth and elevated risk of cardiovascular disease remains unclear" (Gale et al., 2002), p 146. In this thesis, ABPI, carotid stenosis and IMT are used as outcome measures of atheromatous load. Also, in view of the differing results for ischaemic and haemorrhagic stroke more sensitive outcome measures are required. In this thesis early life influences on WML and cortical disconnection as measured by DTI are examined.

1.3 Life course perspective: Genetic and environment interactions

In this introduction the changes in the brain and cognitive function with age, including the importance of cerebrovascular disease, have been described. The literature which suggests that both cognitive ability and cerebrovascular disease are related to conditions in early life has been reviewed. Any influence from early life accounts for only a small proportion of the variance in cognitive ability or cerebrovascular disease, but is important as understanding of the underlying biological mechanisms may allow interventions very early in development to improve cognitive ability and/or reduce morbidity. It is important that researchers considering influences on health and disease in later life do not view early or later life in isolation, but rather take a life course perspective. Life course epidemiology is:

> "...the study of long-term biological, behavioural, and psychosocial processes that link adult health and disease risk to physical or social exposures acting during gestation, childhood, adolescence, earlier in adult life, or across generations." (Kuh et al., 2004a) (p. 3).

Two different models of life course epidemiology have been proposed. Firstly, influences during critical periods of growth pre or postnatally biologically 'programme' adult chronic disease or risk factors. These may or may not be modifiable by later experience. Secondly, cumulative differential lifetime exposures to damaging physical and social environments results in chronic disease. Poor socioeconomic circumstances cause risk factors to cluster together. These models are not mutually exclusive, and may operate simultaneously. The challenges for research in life course influences on health and disease are to integrate social and biological risk processes to investigate how social factors can influence biology and behaviour (Kuh et al., 2004a).

In considering life-long social and environmental influences it is also important to consider the role of genetics. For example, for intelligence, genetic factors account for 40 – 70% of the variance in IQ scores (Neisser et al., 1996; Gottfredson, 1997; McGue, 1997) and that this proportion increases with age, from 20 – 40% in childhood to over 60% age 70 – 80 (Devlin, Daniels, & Roeder, 1997; McClearn et al., 1997). Genetic influences are mostly on the general cognitive factor (*g*) but also

have some effect on specific abilities, particularly memory, and also verbal and spatial ability (McClearn et al., 1997).

No single gene is responsible for age-related cognitive change, and genetic influences are likely to be due to a large number of genetic differences each with a small effect (polygenic), and a smaller number of larger effects (oligogenic effects) (Deary, Wright, Harris, Whalley, & Starr, 2004c). Several genes have been studied in relation to cognitive decline. The most commonly studied is the e4 allele of the gene for Apolipoprotein E (*APOE*), which is associated with increased incidence of Alzheimer's disease, early death, cardiovascular disease and stroke (Smith, 2002). There is evidence of a small influence of *APOE* on normal cognitive ageing, with e4 carriers performing less well in tests of global cognitive ability and episodic memory (Small, Rosnick, Fratiglioni, & Backman, 2004). This is discussed further in Chapter 6.3.1.

APOE alters circulating levels of cholesterol, and its association with cardiovascular disease has therefore been examined. Overall, it is not considered a major risk factor for hypertension, peripheral vascular disease (Resnick et al., 2000), or stroke, (Slooter et al., 2004) but it is the gene most strongly related to normal cholesterol variability (Eichner et al., 2002). Some studies (de Leeuw et al., 2004), but not others (Kuller et al., 1998) have found an association between the e4 allele and WML, and there is also conflicting evidence for carotid atheroma (Elosua et al., 2004; Souza et al., 2003; Fernandez-Miranda et al., 2004).

Around one quarter of the population carry the e4 allele, therefore polymorphisms in this gene are common enough to study in a sample of around one hundred people. We investigated the influence of *APOE* on cognitive function and cerebrovascular risk factors and disease in the Simpson's cohort.

In this thesis, therefore, life course influences on cognitive ability and cerebrovascular disease in a well-characterised cohort of older people are examined. This includes (1) birth weight and other measurements (length and placental weight)

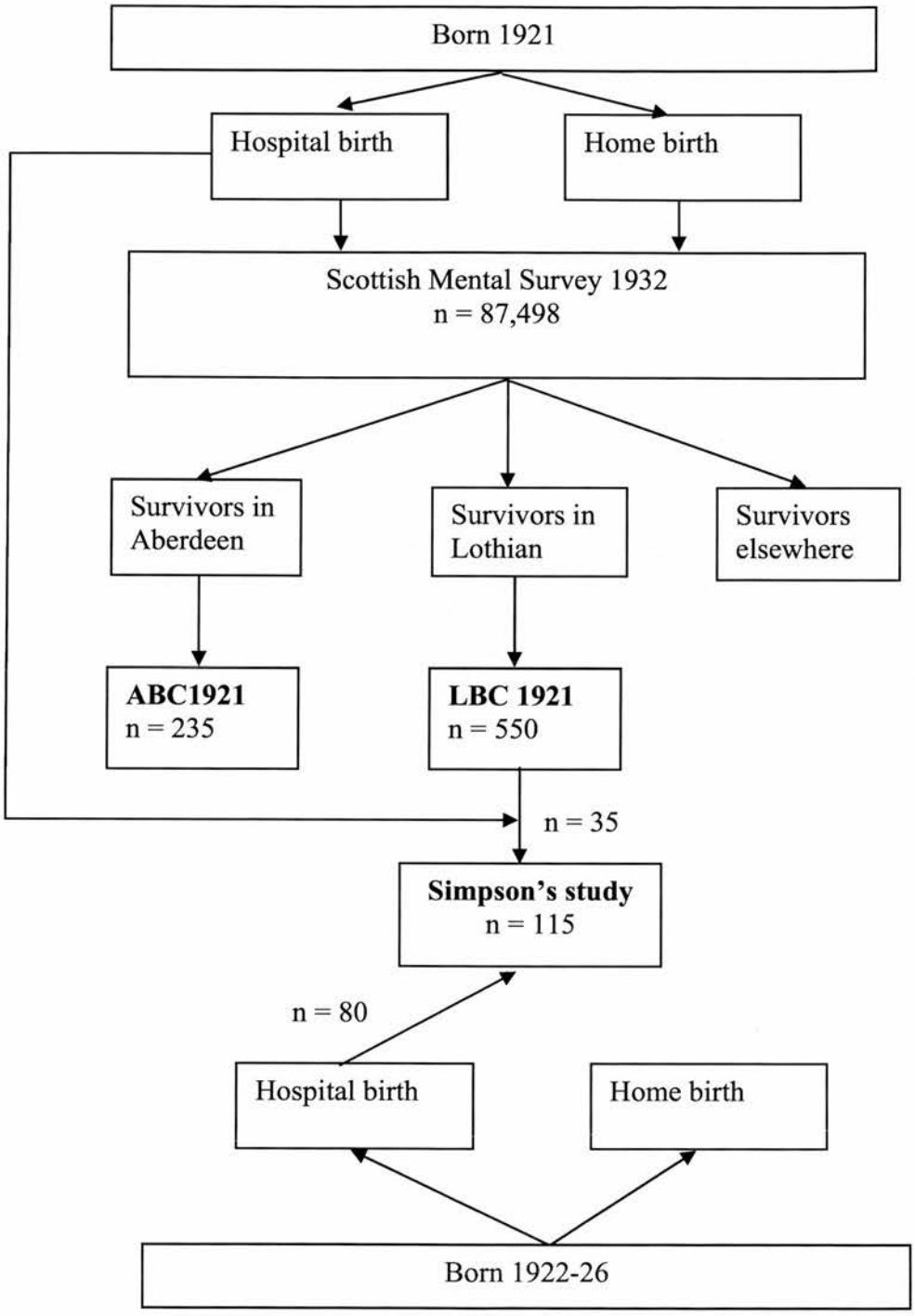
(2) socio-economic environment and (3) genetic influence (*APOE*). Chapter 2 describes the methodology of recovering the archival data, and acquiring cognitive, physical and imaging data. Chapter 3 details the descriptive statistics on the cohort. Chapters 4 and 5 present the results of the cross-sectional study of the relationship between cognitive ability and brain structural imaging (volume, WML and DTI parameters). Chapters 6 and 7 include the retrospectively collected birth data, and investigate the relationship between birth parameters, social class, *APOE* and cognitive ability (Chapter 6), and cerebrovascular disease and vascular risk factors (Chapter 7). Each individual chapter includes a reprise of the relevant literature, methodology and results, and a discussion of the main results in that section. Chapter 8 provides an overall summary with discussion of methodological issues and suggestions for future research.

2 Methods

The research design was based on the discovery of the results of a nationwide test of cognitive ability, the Scottish Mental Survey 1932 (SMS 1932), taken by 11-year-old children in Scotland born in 1921 (described in more detail in Chapter 2.2 below). This resulted in two parallel studies of cognitive ageing that assessed the influences on cognitive change over the lifespan: the Aberdeen and Lothian Birth Cohorts 1921 (ABC 1921 and LBC 1921 respectively, described in (Deary, Whiteman, Starr, Whalley, & Fox, 2004b). These studies collected data in later life (around age 80) for people born in 1921. The Simpson's study was designed to consider the importance of early life influences on cognition. This was made possible by the additional discovery of birth records from Edinburgh hospitals from 1921 (see Chapter 2.1 below and Figure 2.1).

The Simpson's study aimed to recruit those in the LBC 1921 who had been born in hospital, and therefore had birth weight and other details recorded. Despite our substantial, varied and repeated efforts we were unable to recruit sufficient numbers, and therefore extended the Simpson's study to include all those born in Edinburgh hospitals between 1921 and 1926. The archives on which the study was based, and more detail on the change in methodology, are described below (Chapter 2.1-2.2 and Chapter 2.4 respectively). The study and the protocol change were approved by the Local Research Ethics Committee (LREC) as an extension to the LBC 1921. Individuals participating in the study gave their informed consent.

Figure 2.1 The Simpson's study's position in studies derived from the Scottish Mental Survey 1932



2.1 Archives: birth records

Birth records from the early 1920s have been preserved by the Lothian Health Services Archive, and are stored in Special Collections at the Main Library, University of Edinburgh. Permission to view the records for 1921 to 1926 was provided by Dr Michael Barfoot, Archivist, and Dr Peter Donnelly, Director of Public Health and Health Policy, Lothian Health Board. The majority of births in the 1920s took place at home, and no record was made of the size of the child. Birth measurements were recorded, and have been preserved, from three institutions:

1) Royal Maternity and Simpson Memorial Hospital (RMSMH), Lauriston Place

2) Elsie Inglis Memorial Hospital

3) The Lying-in Institution

The data available from these three institutions are summarised in Table 2.1 and described below.

Table 2.1 Data available from hospitals recording birth weight 1921-1926

Hospital	Dates preserved	No. of beds	Child data	Maternal data
RMSMH	1847-1970	94	date of birth sex condition delivery weight length placenta umbilical cord	age address parity LMP whether married husband's occupation
Elsie Inglis	1926-31	40-50	date of birth sex weight length method of feeding	age address parity LMP whether married husband's occupation
Lying-in	1825-1931	4	date of birth sex of child weight of child	age address pregnancy duration

2.1.1 The Royal Maternity and Simpson Memorial Hospital

Records from the Royal Maternity and Simpson Memorial Hospital (RMSMH) have been preserved from 1847 to 1970. The hospital had 94 beds (Tait, 1974) and covered most of the in-patient births in Edinburgh: for example in 1921, 14% of all births in Edinburgh were in hospital (HMSO, 1921), and 11.3% (1,029 of 9,028) were in the RMSMH. Details of the births were recorded in two ledgers, the register of births and the indoor case book. Data recorded (in the birth register, apparently in one person's handwriting, presumably a senior nurse or midwife, and in the indoor case book by the resident house surgeon) included date of admission; date of birth; time of delivery; presentation and position of child; sex; condition of child at birth; mother's name and age; number of previous miscarriages and labours; number of current pregnancy; date of last menstrual period (LMP) (allowed gestational age to be calculated); weight and length of child; weight of placenta; length of umbilical cord; father's name (if legitimate) and occupation; date and place of marriage; last place of residence; discharge date and condition of mother and baby.

Data from every live birth in the Simpson in 1921 was collected and checked by Mrs Margaret Rush, an experienced research associate, who transcribed the information directly to an Access (Microsoft™ 1997) database in a portable computer. Any discrepancies between the two sources were noted, and the birth register data used. It should be noted that some of the birth weights were recorded in grammes. More details on the construction of the 1921 birth database, including reliability and validity, are given in the MSc dissertation (Shenkin, 2002).

The child's name was not recorded in the RMSMH birth register or indoor books. To identify the child's full name Mrs Margaret Rush traced their birth certificate at Register House, Edinburgh. This required a search of birth certificates on microfiche, using the child's date of birth and parents' names. If a potential match was found, this was confirmed if the place of birth recorded on the birth certificate was the RMSMH. If any discrepancies between the RMSMH's records and the birth certificate were noted, such as different father's name or occupation, these were

recorded, and birth certificate information assumed to be correct, as this was an official document.

Those born between 1922 and 1926 were asked to provide their place and date of birth, and parents' names, when volunteering. Their individual record was retrieved with their permission, the details were copied onto a paper proforma, and the record was entered into the database by myself.

2.1.2 Elsie Inglis Memorial Hospital

This hospital opened in 1925 and had 40-50 beds. The register of patients is available from 1925 to 1931, but the postnatal register that includes birth measurements only starts in November 1926, therefore only births after this date have birth measurements recorded. Although various records exist from 1903 to 1988, no other records include birth measurements from the 1920s.

The data recorded in the register included date of admission; date of birth; sex of child; mother's name and age; number of current pregnancy; weight and length of child; father's name (if legitimate) and occupation; address; date of discharge; method and frequency of feeding (breast or bottle); condition of mother and baby at postnatal visit (about 10 days after discharge). With the subject's permission, these data were copied onto a paper proforma and entered into the database by myself.

2.1.3 Lying-in Institution

This small institution existed in various locations from 1825 to 1931: in 1921 it was in Lauriston Place in where it had only 4 beds. Founded by Dr John Thatcher, an eminent obstetrician, in 1825, it was run by his son and then grandson till his death in 1933. Inscribed in the birth register is its mission:

> "...a Dispensary established for affording Advice and Medicines, gratuitously, in the Diseases of Women, Infants, and Children, and for attending Poor Married Women during In-Lying"

Data recorded included date of birth; sex of child; mother's name, age and address; duration of pregnancy in months; weight of child. With permission this information was retrieved from the ledger and transcribed to the database by myself.

2.2 Archives: Scottish Mental Survey

All children born in 1921 who attended school in Scotland on 1st June 1932 participated in the Scottish Mental Survey 1932 (SMS 1932). Some were tested a few days later. The Scottish Council for Research in Education (SCRE) instituted this nation-wide survey of the intelligence of the entire population of Scottish children. It was initially planned to assess the extent of 'mental deficiency' in Scotland by surveying a representative sample of the population, but levels of co-operation were so high, and the difficulties in selecting a truly representative sample so great, that a survey of the entire population was undertaken (The Scottish Council For Research in Education, 1933).

The test used in the SMS 1932 was a group-administered mental ability test, a version of the Moray House Test No. 12 (MHT), designed by Sir Godfrey Thompson. 87,498 children sat the test, only excluding those who were absent on that day, attending a small number of private schools, blind, or attending a facility for the 'mentally handicapped.' This test is very similar to that used in the 11- plus examination, and tests mainly verbal ability (typical questions are shown in the Preliminary Practice Test given to the students, Appendix 9.2). The MHT consists of 71 items, with a maximum score of 76. The items are following directions (14), same-opposites (11), word classification (10), analogies (8), practical items (6), reasoning (5), proverbs (4), arithmetic (4), spatial items (4), mixed sentences (3), cypher coding (2). The MHT was validated by individually retesting 1,000 pupils using the Stanford revision of the Binet- scale, the then gold standard for individually-administered mental ability tests. Correlation between the two scores was 0.76 (The Scottish Council For Research in Education, 1933).

The rich information from the SMS 1932 were rediscovered fortuitously in 1996 due to collaboration between Professor Lawrence Whalley, Department of Mental Health, University of Aberdeen and Professor Ian Deary, Dept of Psychology, University of Edinburgh (Deary, 2000a). All the ledgers were still present in the Council's offices in St John Street, Edinburgh, except for the records from Fife, Wigtown and Angus which have still not been traced. Over several months each child's name, date of birth, school attended and result was transcribed, and ultimately

a large SPSS (SPSS Inc, Chicago, Ill, USA) database of the name, date of birth, school and test score of the majority of the 87,498 records was constructed.

Initially, the birth records were matched to the SMS 1932 to assess the importance of birth characteristics for childhood mental ability in this sample. 529 (53.7%) matches were identified of whom 490 had valid scores. For the results of these analyses and more information on the matching process see Shenkin, 2002; Shenkin et al., 2001.

Those born after 1921 did not participate in the SMS 1932 and therefore had no recorded childhood mental ability score. Their childhood mental ability was estimated using the National Adult Reading Test (NART) (Nelson & Willison, 1991): see Chapter 2.5.3.

2.3 Recruitment: 1921 born

Our initial research protocol included attempting to trace as many people as possible who had been born in the Royal Maternity and Simpson Memorial Hospital in 1921 and who were resident in Lothian from 2000.

An attempt was then made to match each Royal Maternity and Simpson Memorial Hospital birth to an identified individual, alive or dead, in the Lothian Community Health Index (CHI). Lothian Health Board provided this index of name, address, date of birth, unique CHI number and current GP. The information for the whole of Lothian was transferred to an 'Access' database by two research assistants for the LBC 1921. The entire database was searched for each Royal Maternity and Simpson Memorial Hospital birth in turn. A match was identified if name and date of birth were identical, or very similar. Birth and marriage addresses were also taken into consideration. For women, if a possible match was found, her marriage certificate was traced at Register House to confirm her maiden name. These individuals were invited to participate in the LBC 1921, but at this stage no mention was made of their place of birth. For ethical reasons we did not wish to directly approach people with the information that they were born in hospital. Many of these births were due to difficult social circumstances including illegitimacy, and the individuals may not have been aware of some details of their early life. We therefore recruited them as a

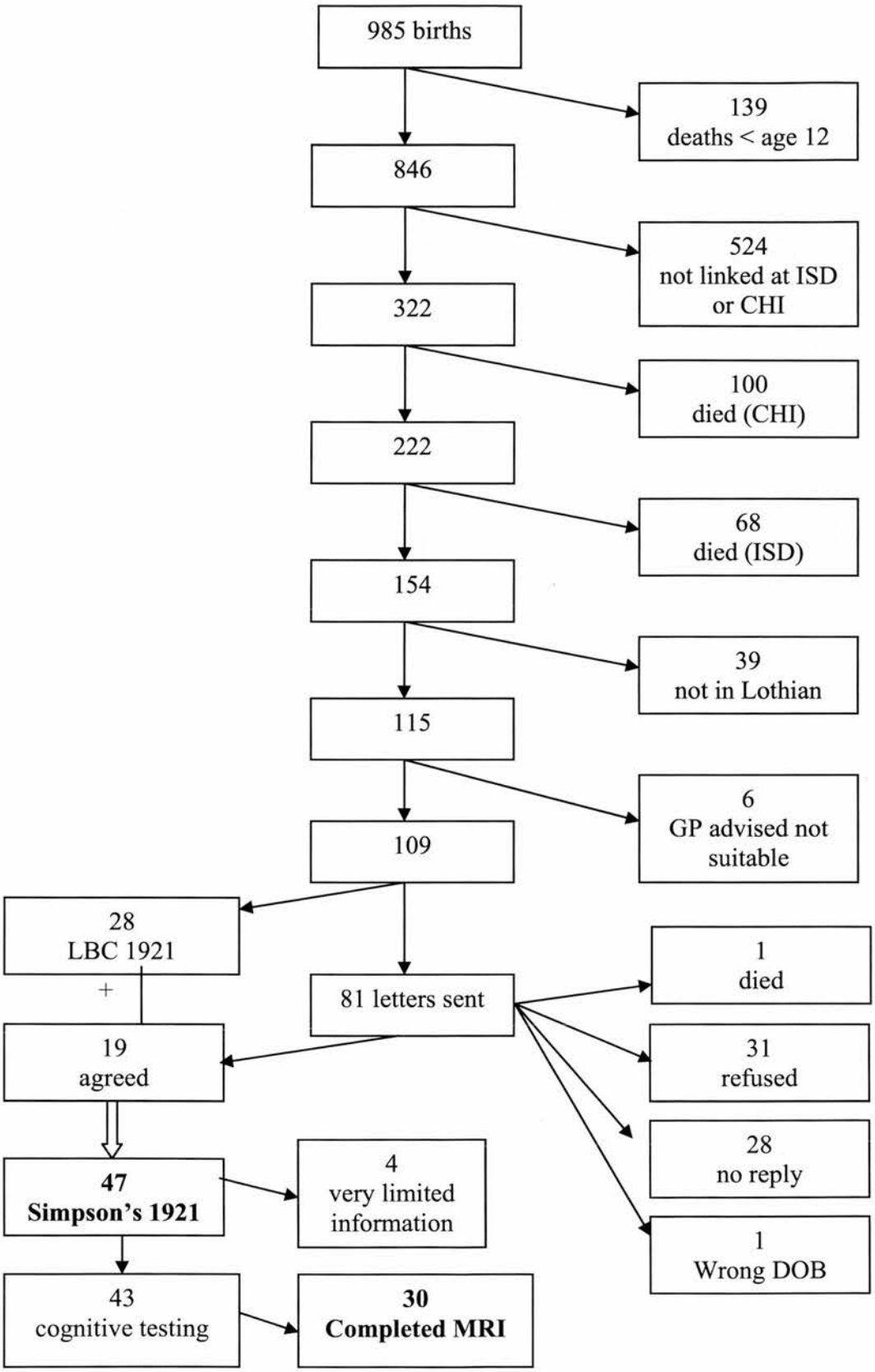
standard LBC 1921 participant, and when they attended asked them if they knew where they were born. All participants knew their place of birth or consented for the birth records to be consulted to confirm whether they were born in hospital. If they were born in hospital the extra tests involved in the Simpson's study were explained, and informed consent was obtained.

For the LBC 1921, participants were recruited from advertisements in the local and national press or by mailing from the research team via an intermediary. In the mailing, letters were initially sent to eligible individuals born in 1921 from a General Practice. The list of those born in 1921 was checked by the GP to ensure invitation was appropriate, and a letter sent to the individuals inviting them to send a reply slip in a stamped addressed envelope to find out more about the LBC 1921 research study. Those who did not reply were sent one reminder letter. The Data Protection Act required a change in strategy, and from 2000 we were required to use Lothian Health Board as an intermediary. The Health Board sent a brief covering letter, and no reminder was permitted.

Those who replied had the study explained on the telephone and had an appointment made for attendance at the Wellcome Trust Clinical Research Facility (WTCRF) at the Western General Hospital for cognitive and physical testing.

The attempts to recruit people to the Simpson's 1921 study are shown in Figure 2.2. The Simpson's study started in July 2000 when 18 people who had attended the LBC 1921 had told the investigators they were born in hospital. Of these, 15 agreed to the extra tests involved in the Simpson's study (ABPI, carotid doppler, brain MRI), including one who refused the MRI due to claustrophobia. A further 29 were recruited to the LBC 1921 (see below) and were told of the Simpson's study during their attendance. Of the 47 people born in RMSM in 1921 4 were not seen and provided limited information (2 unwell, 1 carer, 1 far away); 43 underwent cognitive testing, but 2 refused the further tests (unwell). 5 were seen at home and were too unwell for further tests. 2 had no scans (1 refused, 1 BPV), 34 consented to scans, and 4 did not complete MRI (2 clautrophobic, 1 metal valve, 1 refused).

Figure 2.2 Attempts to trace all births in Royal Maternity and Simpson Memorial Hospital in 1921



Therefore 43 people born in the Royal Maternity and Simpson Memorial Hospital in 1921 participated in the LBC 1921, and 35 agreed to the extra tests in the Simpson's study, with 30 ultimately completing the MRI. This number fell short of the number we had initially hoped to recruit based on the proportion of births in hospital. The Lothian Community Health Index (CHI) in 1999 identified 6,058 people registered with a GP in Lothian. A further 2,615 were recorded in the CHI as dead. As 14% of the population were born in hospital in 1921 we might have expected around 1,200 of the total 8,673 listed in the CHI to have been born in hospital, but not all of these would have been born in the Edinburgh area. We took each of the 985 individuals born in the RMSMH in 1921 and tried to match it with the CHI, confirming a match if name and date of birth were identical. We matched 224 individuals, of whom 100 had died when the study started in July 2000, and 28 had already participated in LBC 1921, or were waiting to attend. Of the remaining 96, GPs excluded six on health grounds, and nine had transferred out of Lothian. 81 further letters of invitation were sent. One person replied who was not born in RMSMH. Of the eighty eligible people invited, 23 agreed (28.7%) (but four of these subsequently withdrew, i.e. 19 agreed), 32 refused, one person had died, and 28 did not reply despite reminders.

A total of 47 people born in the RMSMH gave some information to the Simpson's study. Three completed questionnaires only, one person was seen in hospital and gave only limited information, and therefore 43 underwent some psychological testing. 39 people had complete test data (four did not complete some tests due to visual impairment or deafness). 34 agreed to scans and completed dopplers, and of these 30 completed the MRI scan (2 aborted for claustrophobia, one contraindicated due to metal valve, one refused).

Because we had traced fewer people than expected, we used the Information and Statistics Division (ISD) of the Common Services Agency to match the names and dates of birth in the RMSMH to the record of hospital attendances and deaths after 1981 in the whole of Scotland. Due to Data Protection concerns, ISD were not able to give us current addresses of people matched, but if substantial numbers were identified we could have applied for permission to approach these people via their

local health boards. They found a further 68 deaths and 39 people alive throughout Scotland. Even if all 39 had agreed to participate we would still have required more volunteers to address our hypotheses, and with a predicted response rate of less than 30% we did not attempt to contact this small group. Furthermore, only 25 of these people had valid SMS 1932 scores.

The shortfall in numbers can be seen on two levels: firstly the smaller than expected cohort identified in 2000, and secondly the low participation rate in those invited to take part. In terms of the relatively small numbers of those born in hospital identified by CHI or ISD, three main reasons were identified. (1) Mortality was extremely high: 139 of the 985 births in the Royal Maternity and Simpson Memorial Hospital had died by the age of eleven, and the mean life expectancy at birth in 1921 was only 53.1 years for men and 56.4 years for women (HMSO, 1921). Because many of the births in hospital were for social reasons, this group may be disproportionately disadvantaged. People who suffer social disadvantage have higher mortality (Osler et al., 2003; Marmot, Shipley, Brunner, & Hemingway, 2001). (2) Many of the children would have been adopted both formally and informally, and may have changed surname or even first name. This does not only include illegitimate births, but many children of this generation were brought up by various family members, especially grandparents, and were often known by nicknames or family names different from those used on official documents. (3) Migration out of Scotland was significant in this period between the First and Second World War. In the 1920s 390,000 more people left the country than entered it (Dickson & Treble, 1998). Some of the women who gave birth in the RMSMH had come from far afield (e.g. one from Ireland, five from England), perhaps specifically for the birth, and were likely to return there. Several people identified in the CHI had moved out of Lothian, and unexpectedly, Lothian Health Board did not have a record of the region to which they had transferred. Without the region in which individuals were living, we were unable to apply to Directors of Public Health in each region to trace these individuals. (4) Also, the Scottish Mental Survey Results ledger for Fife has not been discovered despite extensive searches, therefore excluding a number of potential participants.

The participation rate in this study was lower than for similar studies conducted previously by this research team, but may reflect the increased morbidity among this group. It is also possible that some people did not wish to participate due to concern about personal details that might be revealed in their birth records. In addition, the inclusion of brain MRI scanning was a factor for several people.

Therefore, one year into the project we realised there would be a shortfall in numbers and a change in protocol was required.

2.4 Recruitment: 1922-26 born

The main aim of this study concerned the relationship between birth measurements and cognitive change including brain scanning, rather than the importance of the childhood mental ability score. As we were unable to recruit enough subjects born in 1921 with both birth weight and childhood mental ability records, we extended recruitment to include people with just birth weight recorded. We included those born in Edinburgh hospitals between 1922 and 1926. These people did not have actual childhood mental ability recorded, but we were able to estimate their childhood IQ using the National Adult Reading Test (NART) which assesses pronunciation of irregularly pronounced words (see Chapter 2.5.3), and correlates highly with childhood IQ r = 0.69 (Crawford, Deary, Starr, & Whalley, 2001). Approval for this change was sought and granted from LREC and the grant awarding bodies (Medical Research Council, Chest Heart and Stroke, Scotland).

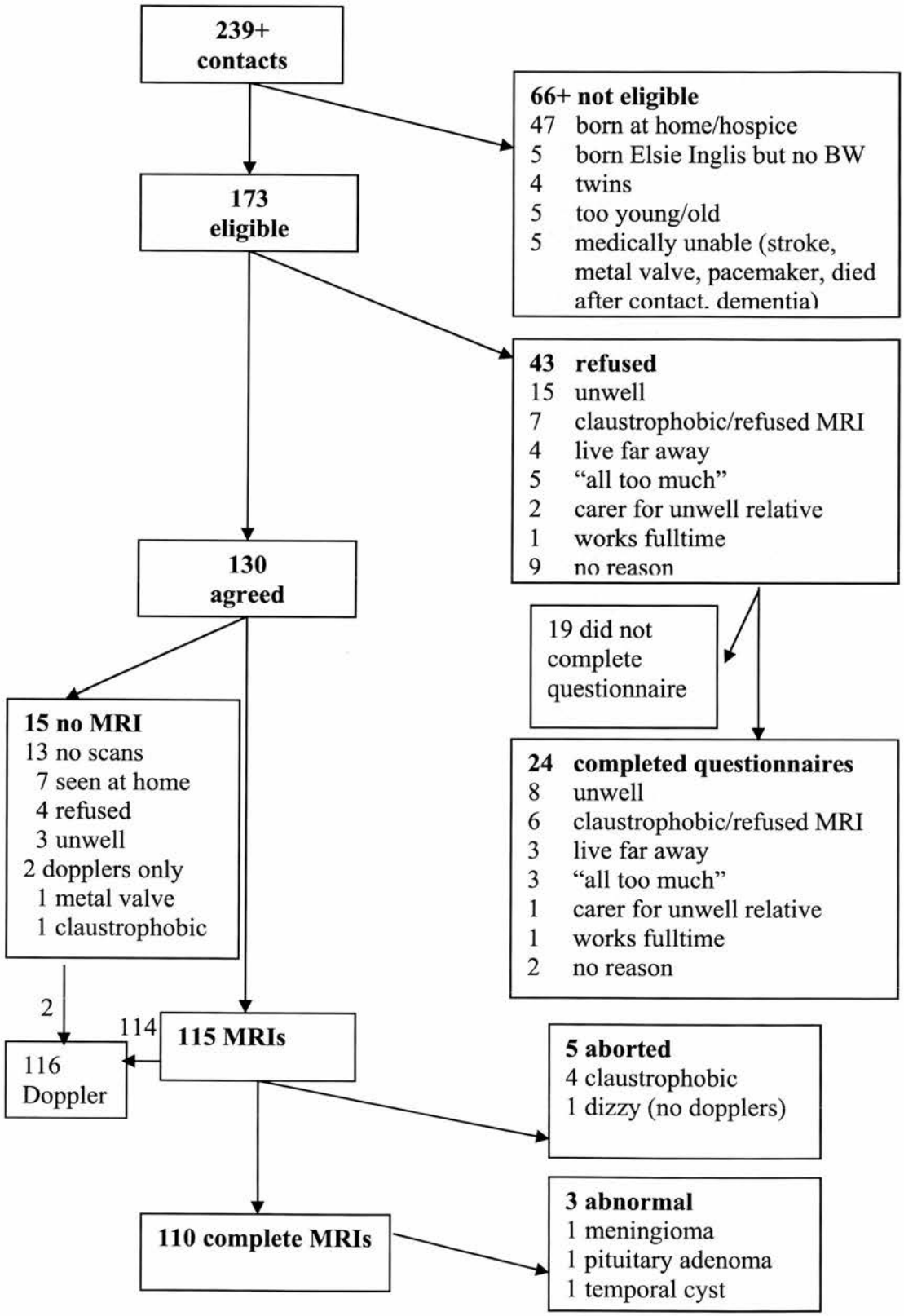
We recruited people born in 1921-26 in hospitals in Edinburgh by appealing for volunteers. This was done in many different ways, including (1) local newspaper adverts and articles, articles in national newspapers, two appeals in the Edinburgh council magazine (distributed free to every home in Edinburgh), and local newsletters (2) posters in all local hospitals (outpatient clinics and care of the elderly wards), libraries and supermarkets (3) a letter to every church, community centre and theatre in Edinburgh asking them to mention the study, and to display a poster (4) letters and/or phone calls to every lunch club, and all leisure clubs mentioned in the Edinburgh council 'Get up and go' booklet (aimed at those 50+) asking them to mention the study, and to display a poster (5) contact with local charities dealing

with older people, asking them to mention the study to volunteers and/or in their newsletters (6) appeals in the newsletters of many of the Royal Colleges (7) contact with the pensioners' societies of the largest employers in Edinburgh asking them to mention the study to their members (8) an email to every student in the psychology department asking them to ask their relatives if they would be interested (9) a letter to every GP in Edinburgh whose patient participated, asking them to display a poster about the study (10) every participant was asked to mention the study to friends and relatives, and also given two posters to display locally.

This strategy avoided concerns of directly approaching individuals using health record data (birth records) without their permission. It ensured that information about their birth was only disclosed to people who were aware of their place of birth (thus avoiding the ethical problem of inviting people who were not aware they were born in hospital, which may have been because their birth was illegitimate, or they were adopted).

Using this strategy we recruited a further 83 people. In total, 130 people took part in the Simpson's study, 115 agreed to MRI scans, and 110 completed scans. The full recruitment flow chart is shown in Figure 2.3: over 239 people contacted us to find out more information, and data about reason for non-inclusion was only recorded for 66 people.

Figure 2.3 Recruitment to Simpson's Study



2.5 Tests: psychometric

These tests were all administered by myself at the Wellcome Trust Clinical Research Facility (WTCRF) (n = 123) or the individual's home (n = 7). The information, consent, and data collection forms are included in Appendix 9.3. The battery of tests was designed for the LBC 1921 to include well-established, reliable, and valid tests that assess various cognitive domains.

2.5.1 Hospital Anxiety and Depression scale (HADS)

The HADS (nferNelson) is a self-administered questionnaire (Zigmond & Snaith, 1983) designed to screen for anxiety and depression in the previous week. It takes only 2-5 minutes to complete, and although it was designed for used in hospital populations it has been validated in other settings (Snaith, 2003). The anxiety and depression subscales each have a maximum possible score of 21. A score of 0-7 is considered normal, 8-10 borderline, and 11 or over indicative of anxiety or depression respectively. It is only validated as a screening tool, and definitive diagnosis requires a clinical examination.

2.5.2 Mini Mental State Examination (MMSE)

The MMSE (Folstein, Folstein, & McHugh, 1975) is probably the most widely used brief screening instrument for dementia. It takes only 5-10 minutes to administer, requires only paper and pencil, and the standardised administration and scoring are easily learned. It is scored out of 30, and scores below 24 have been considered abnormal for screening for delirium or dementia (Lezak, 1995). It has a pronounced ceiling effect, with many people still scoring 30 despite substantial cognitive impairment, and norms vary according to age and educational level (Crum, Anthony, Bassett, & Folstein, 1993).

2.5.3 National Adult Reading Test (NART)

In the National Adult Reading Test (NART) (Nelson et al., 1991) participants are shown a type-written list of 50 irregularly pronounced words (e.g. chord, syncope) and asked to read them aloud. The number of errors is recorded (out of 50). As the pronunciation cannot be guessed using normal grapheme-phoneme rules, correct

pronunciation reflects previous learning of this word. Performance on the NART correlates highly with full scale IQ as measured by the Wechsler Adult Intelligence Scale (Lezak, 1995). In healthy populations scores on the NART correlate more highly with verbal IQ than with performance IQ (Crawford & Allan, 1997; Crawford et al., 1989). The NART has been used in clinical settings such as a means of estimating 'premorbid' IQ in patients with mild dementia. It is also used in the study of healthy older people to estimate peak childhood or adulthood ability ('prior' IQ), as scores correlate highly with IQ scores in childhood and adulthood (Crawford et al., 2001). In the Simpson's study the NART score is recorded as a positive score: 50 – the number of errors.

2.5.4 Verbal Fluency

The most commonly-used test of verbal fluency is the Controlled Oral Word Association Test (Benton and Hamsher, 1989 in Lezak, 1995), previously called the Verbal Associative Fluency Test and the Controlled Word Association Test (Lezak, 1995). The examiner asks the participant to say as many words as possible, in one minute, which begin with a certain letter. Proper nouns, numbers, and the same word with different suffixes are not permitted. The letter S was used to practice, to ensure the task was understood before being scored, then the letters C, F and L were used. These are standard letters selected for their frequency in English. Words said were recorded on paper, and the score from this test was the simple sum of the number of words produced. A score of 53+ is superior, 45-52 high normal, 31-44 is normal, 25-30 low normal, 23-24 borderline, 17-22 defective, 10-16 severe defect, and 0-9 nil-trace (Lezak, 1995). This test has been shown to be sensitive to damage to the frontal lobe (Lezak, 1995) and is often considered a test of 'executive' or 'frontal lobe' function. Performance declines with ageing, and also in dementia (Lezak, 1995).

2.5.5 Raven's Standard Progressive Matrices

Raven's Standard Progressive Matrices (RSPM) is a test of non-verbal reasoning which consists of a series of visual pattern matching and analogy problems shown in abstract designs (Raven, Court, & Raven, 1977). RSPM is thought to be one of the best tests of fluid intelligence and loads highly on to the general cognitive factor (*g*) (Carroll, 1993). There are 60 items organised in five groups of 12. Subjects were

given 20 minutes to complete as much of the test as possible and the score was the number correct. Performance on RSPM shows decline with ageing (Carlson & Jensen, 1981) and with dementia (Gainotti, Parlato, Monteleone, & Carlomagno, 1992).

2.5.6 Moray House Test (MHT)

This test was previously described in the context of the Scottish Mental Survey 1932 (Chapter 2.2). The participants in the Simpson's study completed the almost identical test that had been used in the Scottish Mental Survey, a version of the Moray House Test No 12 (The Scottish Council For Research in Education, 1933). The MHT was originally validated as a group administered test of verbal ability for children, but had not previously been formally validated for individual administration to adults aged over 75. The Aberdeen and Lothian Birth Cohorts, however, showed that this test was acceptable to older people, had a wide range of results (although some ceiling effect) and correlated well with the individual's childhood result ($r = .64$) (Deary et al., 2004a; Crawford et al., 2001; Deary et al., 2000).

2.5.7 Logical Memory

The Logical Memory subtest of the Wechsler Memory Scale – Revised (Wechsler, 1987) tests verbal memory. Two short stories, each comprising 25 'memorable ideas', are read aloud. After each story the participant is asked to recall as much of the story as possible. After a delay of 45 minutes they are again asked to recall as much of each story as possible. Ageing and dementia are both associated with reduced scores in Logical Memory (Lezak, 1995). In the Simpson's study, the total Logical Memory score (total of the immediate and delayed recall of the two stories: maximum 100) is used.

2.6 Tests: physical

The data collection forms are included in Appendix 9.3. Individuals were asked if a doctor had ever told them that they had: hypertension (high blood pressure), diabetes, heart disease, stroke, or "mini-stroke" (transient ischaemic attack - TIA), peripheral or other vascular disease, thyroid disease, cancer, dementia, or other significant illness. Details were sought for positive responses. In addition, details of current medication were recorded, whether they were an ex, current or never smoker, and

age started and stopped, and average number of cigarettes per day. Average alcohol consumption over a week was also assessed and recorded in units.

The nursing staff at the WTCRF administered the physical tests adhering to standard operating procedures. All procedures and equipment were checked annually. Height was measured without shoes using a standard stadiometer, weight measured on electronic scales (Seca Model 797) with shoes and outdoor clothing removed. Demispan was measured from the sternal notch to the tip of the middle finger. Dentition was assessed by asking the individual to count the number of remaining teeth, and if they had no teeth, when they lost their last tooth. A six metre walk was timed using a stopwatch, vision was assessed using a standard Snellen chart. Blood pressure was measured, using a Dinamap Compact Monitor automated blood pressure machine (Critikon), after a two-minute rest lying and then after standing for one minute. Grip strength was the best of three attempts in the dominant hand, passing the hydraulic hand dynamometer (North Coast Medical, Inc.) from hand to hand. Pulmonary function (FEV1, PEFR, FVC, and FER) was the best of three attempts using a Micromedical spirometer. Functional dependence was assessed using the Townsend score (Townsend, 1979). Ankle brachial pressure index (ABPI) was measured using a Dopplex® advanced pocket doppler VP4 (Huntleigh Diagnostics). Pressures at right and left brachial, posterior tibial and dorsalis pedis arteries were recorded. A resting 12 lead electrocardiogram (ECG) (Marquette MAC 1200) was also recorded.

Blood samples were also taken for HbA_{1c}, cholesterol, triglycerides, thyroid function tests (TSH, T_3, T_4), full blood count (Hb, WCC, platelets), clotting (fibrinogen, PT, APTT), vitamin B12 and serum folate. These samples were analysed in a standard way in the Western General Hospital clinical chemistry and haematology laboratories.

2.6.1 Apolipoprotein E genotyping

Samples were each given an anonymous label and stored in the genetic core of the WTCRF for future genetic analysis. In February 2004 all samples were genotyped for Apolipoprotein E. This was done by staff in the genetics core of the WTCRF, and

their methodology is described in Appendix 9.4. Briefly, this involved PCR amplification of a 227-bp fragment of the *APOE* gene containing two polymorphic sites, which account for the three alleles e2, e3 and e4 (Wenham, Price, & Blandell, 1991). Genotyping was carried out on the Taqman 7900 machine. The WTCRF provided the 'call' for the single nucleotide polymorphism (SNP) for each allele from which the resultant allele was determined (with assistance from Dr Caroline Hayward at the MRC Medical Genetics Unit), and entered in the database.

Results from those who had participated in the LBC 1921 study (n = 45) had been analysed in the MRC Clinical Genetics unit, where the alleles were distinguished by restriction digest of the PCR products with *Cfol* followed by electrophoresis in 4% Nusieve gels, and were available from the LBC 1921 study investigators.

2.7 Social variables

Participants were asked where they were born, where they attended school, age at leaving school, and any further full-time education. Their years of full-time education were recorded. Their employment history and that of their spouse was recorded, and the highest occupation was coded for social class (for married women her husband's occupation was coded) (see Chapter 2.9). In addition they were asked whether or not they currently own their home, and number of hours of home help they require.

To assess their childhood circumstances they were asked to recall for when they were aged 11: their parents' jobs, home address, the number of rooms (not including bathrooms/toilets or cupboards) and number of people sharing these rooms (allowing calculation of an overcrowding index), and whether or not they had an indoor toilet, and the number of people who shared this. Also, they were asked whether they knew of their birth weight, and the age and cause of parents' death.

The full session took an individual about 3½ hours, including breaks. The volunteer could specify morning or afternoon, and up to two people could attend each session. At the end of the session they received a certificate of thanks for their participation

which recorded their birth measurements. They were then asked to return at a future date for the scans.

2.8 Imaging variables

2.8.1 Carotid doppler ultrasound scans

Carotid doppler scans were performed using a 5-7MHz probes operating in colour Doppler mode (Acuson 128xp 10 v until summer 2002, Siemens Elegra subsequently). All scans were performed in the Department of Clinical Neurosciences, Western General Hospital by Mrs Elizabeth Eadie (n = 109) and Professor Joanna M Wardlaw (n = 7). The operators were blind to all data collected for the study, including the MRI scans. On longitudinal 2-D B-mode images the following measurements were made: (1) degree and site of maximum stenosis (2) any vertebral artery abnormality (3) intima media thickness and (4) intima adventitia thickness. Details of the methodology (Zwiebel, 1992; Pignoli, Tremoli, Poli, Oreste, & Paoletti, 1986; Wendelhag, Gustavsson, Suurkula, Berglund, & Wikstrand, 1991; Kanters, Algra, van Leeuwen, & Banga, 1997), and the paper proforma for recording the results, are given in Appendix 9.5.

2.8.2 Magnetic Resonance Imaging (MRI)

All scans were performed using a GE Signa LX 1.5 T (General Electric, Milwaukee, WI, USA) research scanner in the SHEFC Brain Imaging Research Centre for Scotland in the Western General Hospital. The images produced were analysed for (1) volumes of whole brain, frontal and temporal lobes, amygdyla-hippocampal complex and ventricles, corpus callosum area and intracranial area (2) white matter lesions and (3) diffusion tensor imaging (DTI) parameters <D> and FA, using regions of interest in frontal and occipital white matter and centrum semiovale. Each scan took approximately 40 minutes. These scanning protocols and methods of analysis were designed and carried out by staff in the SHEFC Brain Imaging Research Centre for Scotland. Methodology for the structural scans is described in detail in Appendix 9.6, and briefly in Chapter 4.1.2 and 4.2.2. The DTI methodology is detailed in Appendix 9.7, and briefly in Chapter 5.2.1.

2.8.3 Mortality statistics

Whether participants had subsequently died or not, and their cause of death, was established by comparing an electronic file of name, date of birth and postcode against the death registers of Scotland on 1st September, 2004 (Mr Ian Brown at General Register House). This identifies a match as 'good' 'possible' or 'no match'. Where a match was identified information in the public domain was provided: date, place and causes of death. This identified 11 'good' matches, 14 'possible' matches of which three matched other details we held. We had also been informed of one additional death which was not identified as a match using this electronic system, therefore four years after the study started there were 15 (11.5%) deaths. The underlying cause of death and ICD-10 code was entered into the database.

2.9 Database construction

All results were recorded on paper forms (Appendix 9.3), and the scores to be entered in the database transferred to a single sheet. The scoring of the cognitive tests was checked by a research assistant (Mrs Alison Pattie), who also checked that the transcription of results to the single sheet was accurate. The data were then entered into a SPSS version 12 database (SPSS Inc, Chacago, Ill, USA): individuals were identified only by a unique number, and all personal identifiers were omitted. The data entered were checked against the paper records. The final database comprised 366 variables (listed in Appendix 9.8).

Some data had to be recoded prior to analysis.

1) Imperial measures were converted to metric: 1 lb = 453g, 1 oz = 28g, 1 inch = 2.5cm.
2) Gestational age was calculated by subtracting date of last menstrual period (LMP) from date of birth, and the number of days divided by seven, omitting the remainder, to give full weeks of gestation. If only month of LMP was given, the gestational age was calculated using the 15th of the month.
3) For social class, occupations were coded using the Registrar General's Classification, obtained from the 1951 Census Classification of Occupations (H.M.S.O., 1956). This divides occupations into five categories:

I Professional e.g. lawyer, doctor, clergyman, professional engineer

II Intermediate e.g. proprietor of business, trained nurse, artist

III Skilled e.g. clerk, policeman, miner, chauffeur

IV Partly skilled e.g. fisherman, carter, stoker, conductor

V Unskilled e.g. labourer, railwayman, watchman

Social class III was subdivided into non-manual (e.g. clerk, policeman) and manual (e.g. miner, chauffeur) using the Classification of Occupations 1970 (H.M.S.O., 1970). Social class coding was checked by Mrs Alison Pattie.

4) ECGs were coded using the Minnesota code (Prineas, Harland, Janzon, & Kannel, 1982). 37 of the ECGs were coded independently by a second researcher (Dr Brian McGurn) to ensure consistency with previous studies.

3 The sample

Descriptive statistics are presented for the 110 subjects who underwent MRI. Descriptive statistics for the whole 130 recruited to the study are shown in Appendix 9.9, along with comparison between the 110 people who underwent MRI scanning and the additional 20 who provided some information.

Table 3.1 Descriptive statistics of 110 subjects

	n	%		
Male	33	30.0		
History of hypertension	49	44.5		
History of cardiovascular disease	37	33.6		
History of thyroid dysfunction	18	16.4		
History cerebrovascular disease	11	10.0		
History of other vascular problems	6	5.5		
History of neoplasia	15	13.6		
History of diabetes	7	6.4		
On medication	98	89.1		
	Mean	**SD**	**Min**	**Max**
Age at testing (years)	78.2	1.4	75.5	81.5
Number of medications	3.3	2.5	0	11

The proportion of participants who self-reported a history of disease are broadly comparable with an American study based in Washington University, St Louis, MO, including 94 non-demented people (71.3% women) mean age 78 (SD 8) years who were paid to participate in an imaging study of brain volume changes with age (Fotenos et al., 2005). 43.0% of these reported hypertension, and 10.8% diabetes. Mean number of medications were 2.9 (SD 2.1).

3.1 Birth characteristics

The vast majority of participants were born in the RMSMH: of the 110 taking part in the final study 109 were born in RMSMH and one in Elsie Inglis. Of the additional 20 who took part in some of the study, all were born in the RMSMH except one, who

was born in the Lying-in Hospital. The data recorded at birth for the baby and mother are presented in Table 3.2.

Table 3.2 Birth characteristics of 110 subjects

Variable	n	Mean	SD	Min	Max
Birth weight (g)	110	3333.6	457.2	2226	4564
Birth length (cm)	107	50.7	2.7	43.2	55.9
Placental weight (g)	83	678.3	145.0	340	1077
Umbilical cord length (cm)	83	57.0	11.7	30.5	104.1
Gestational age (weeks)	100	39.5	2.5	30.3	45.3
Maternal age (years)	110	28.0	6.4	18	46
	n	**%**			
Pregnancy number				1	9
1	57	51.8			
2	25	22.7			
3	7	6.4			
4 or more	21	19.1			
Illegitimate	10	9.1			
Legitimate births social class					
I	2	2.0			
II	9	9.0			
IIIN	16	16.0			
IIIM	45	45.0			
IV	16	16.0			
V	12	12.0			

3.2 Cognitive tests

Results of the cognitive tests and Hospital Anxiety and Depression Score are presented in Table 3.3. Full data were not obtained for all tests: MMSE was omitted on one individual due to profound deafness, and on two subjects it was used to exclude severe global cognitive impairment, but not included in analyses (one registered blind person scored 26/28, one registered partially blind person scored 28/29). One man was unable to do the logical memory test due to profound deafness. The two people with visual impairment did not attempt the RSPM or the MHT. One

subject continued the RSPM for 27 minutes due to a timing error, and their score was excluded. MHT has the lowest number of complete scores: one person did not attempt the test (insufficient time available) and three missed a page, and were therefore excluded (scored 59/73; 51/62; 51/67).

Table 3.3 Cognitive test results for 110 people taking part in Simpson's study

Test	n	Mean	SD	Min	Max
MMSE/30	107	28.3	1.4	24	30
HAD-anxiety/21	110	5.2	3.2	0	14
HAD-depression/21	110	3.8	2.3	0	10
Logical Memory Total /100	109	32.9	11.7	6	74
NART (positive score) /50	110	29.9	7.9	11	44
Raven's SPM /60	107	30.8	8.2	12	51
Moray House Test /76	104	57.4	8.7	30	74
Verbal fluency (total)	110	37.2	12.3	15	78

All cognitive tests were positively intercorrelated (Table 3.4).

Table 3.4 Correlation matrix of cognitive tests (Pearson's r)

Test	MMSE	LM	NART	RSPM	MHT
LM	.13	-	-	-	-
NART	.28*	**.19**	-	-	-
RSPM	.26	**.26**	**.30***	-	-
MHT	**.27***	**.22**	**.57***	**.69***	-
VF	**.23***	.15	**.44***	**.23**	**.43***

Bold type: P <.05 *P <.01 n = 103 to 110 (see Table 3.3)
Test scores using standardised residuals corrected for age in days

Principal components analysis was therefore used to derive a general cognitive factor (*g*) from the tests of more fluid ability (Verbal fluency, RSPM, Moray House Test, Logical Memory). The first unrotated principal component accounted for 51.3% of the total variance (initial eigenvalue 2.05), with factor loadings on RSPM .82, MHT .89, VF .61, LM .47. Each subject was given a score on this general cognitive factor (*g*), in addition to NART and MMSE scores.

3.3 Physical tests

The descriptive statistics for the physical tests are presented in Table 3.5, divided by sex because the overall means will be affected by the sample's sex mix. One female subject did not have demispan measured. One was unable to stand for blood pressure.

Table 3.5 Physical and blood tests for 110 subjects (male n = 33)

	Male				Female			
Variable	**Mean**	**SD**	**Min**	**Max**	**Mean**	**SD**	**Min**	**Max**
Weight (kg)	75.2	11.7	49.4	98.0	66.9	11.3	45.4	95.6
Height (cm)	167.8	6.5	155.4	181.8	155.1	5.8	144.0	169.0
Demispan(cm)	79.5	4.0	72.5	90.0	72.4	3.8	63.0	83.0
Sitting BP (mmHg)								
systolic	161.2	29.9	108	238	157.7	23.7	103	226
diastolic	82.0	15.0	54	110	77.7	11.3	54	124
Standing BP (mmHg)								
systolic	158.3	30.7	110	244	155.1	24.9	94	222
diastolic	85.2	13.1	62	114	77.9	13.3	50	123
FEV1	2.4	0.55	0.75	3.14	1.6	0.4	0.7	2.4
FVC	3.05	0.6	1.5	4.0	2.1	0.4	1.2	3.2
FER	80.6	11.5	43	100	82.3	10.5	38	101
Peak flow	354.5	124.7	92	601	227.5	77.9	42	410
Grip (kg)	32.2	6.0	14.0	42.0	20.2	5.6	6	36
6m walk (s)	4.5	1.3	2.8	8.4	5.5	2.0	3.0	13.3
ABPI	0.94	0.21	0.57	1.63	0.89	0.18	0.40	1.16
Cholesterol	4.9	.97	3.3	7.1	5.7	1.0	3.8	8.8
HbA_{1c}	5.7	.59	5.0	8.1	5.9	.67	4.3	8.7
Fibrinogen	3.2	.76	2.0	5.9	3.4	.75	2.0	5.3

The mean blood pressure is higher than the sample (mean age 78, SD 8 years) in the American imaging study (Fotenos et al., 2005) (mean systolic BP 136, SD 18, mean diastolic BP 73, SD 10 mmHg).

3.4 Apolipoprotein E

The Apolipoprotein E genotype frequencies are shown in Table 3.6. One participant did not wish to have blood stored (Jehovah's witness), and four further samples

failed on the run and no genotype could be determined. *APOE* allele status was therefore determined on 105 (95.5%) of the 110 who had scans. The *APOE* genotype frequencies are shown below.

Table 3.6 *APOE* genotypes on 105 of 110 subjects

***APOE* genotype**	**n**	**%**
e2e2	1	0.9
e2e3	15	13.6
e2e4	4	3.6
e3e3	55	50.0
e3e4	30	27.3
Total	105	

Allele frequencies of the sample were therefore e2 = 8.8%, e3 = 69.6%, e4 = 16.2%, similar to other, more representative samples from Aberdeen and Glasgow (Cumming & Robertson, 1984; Deary et al., 2003a). No subjects possessed two *APOE* e4 alleles, 34 (30.9%) were *APOE*e4+ and 71 (64.5%) were *APOE*e4-. The sample is in Hardy Weinberg equilibrium ($X^2 = 3.92$, df = 2, P >.1) (Christensen, 2005); i.e. the sample is not significantly different from the expected population. This means there is random mating with respect to this locus, and no genotype selective advantage.

3.5 Social information

Social class was coded into five social classes using the Registrar General's Classification of Occupations 1951, and then Social Class III was divided into manual and non-manual using the Classification of Occupations 1970. Descriptive statistics are presented separately for men and women in Table 3.7.

Table 3.7 Social information for 110 subjects (male n = 33)

Variable	Male Med	I/Q range	Min	Max	Female Med	I/Q range	Min	Max
Full-time education (yrs)	10.0	9.0, 12.5	8.5	22.0	9.0	7.0,16.0	7.0	16.0
Alcohol (units per wk)	6.0	6.0, 18.5	0	43.0	1.0	1.0, 3.5	0	17.0
Number of teeth	4.0	0, 16.5	0	27.0	0	0, 13.5	0	27.0
	n	**% of men**			**n**	**% of women**		
Lives alone	7	21.2			49	63.6		
Home help	5	15.2			8	10.4		
Lives in - own home	30	90.9			60	77.9		
- rented	3	9.1			13	16.9		
- sheltered	0	0			4	5.2		
Smoking - current	2	6.1			6	7.8		
- ex	12	36.4			38	49.4		
- never	19	57.6			33	42.9		
Social class								
- I	5	15.2			5	6.5		
- II	13	39.4			23	29.9		
- IIIN	4	12.1			16	20.8		
- IIIM	11	33.3			30	39.0		
- IV	0	0			1	1.3		
- V	0	0			2	2.6		

Med = Median I/Q range = interquartile range

3.6 Imaging

Results from the carotid doppler ultrasound scans are presented in Table 3.8. For the vertebral arteries two on the right and one on the left were not seen, therefore the number of abnormal vertebral arteries were right 6/108 and left 6/109.

Table 3.8 Carotid doppler results for 110 subjects

Variable		n	Mean	SD	Min	Max
Right IMT		110	.90	.19	.50	1.60
Left IMT		110	.96	.24	.50	2.20
Mean IMT		110	.94	.18	.50	1.65
Right IAT		110	1.51	.27	.90	2.50
Left IAT		110	1.58	.35	1.00	2.90
% stenosis	**Right**	**n**	**%**	**Left**	**n**	**%**
0-20		74	67.3		75	68.2
21-40		20	18.2		26	23.6
41-60		8	7.3		3	2.7
61-80		6	5.5		4	3.6
81-99		1	.1		2	.2
100		1	.1		0	
Vertebral artery abnormal	**Right**	6	5.5	**Left**	6	5.5

IMT = intima media thickness IAT = intima adventitia thickness

The volumes for whole brain, ventricles, frontal and temporal lobes, amygdalo-hippocampal complex, and intracranial area, are shown in Table 3.9.

Table 3.9 Neuroimaging results (area and volumes) for 110 subjects

Variable	Mean	SD	Min	Max
Whole brain volume (cm^3)	1137.5	98.0	947.4	1405.3
Corpus callosum area (mm^2)	540.6	83.0	392.0	775.2
Intracranial area (cm^2)	148.9	10.4	129.3	173.7
Ventricular volume (mm^3)	30781.0	18912.2	4655.7	96263.5
Right frontal lobe volume (mm^3)	55880.5	8095.4	38878.7	77656.7
Left frontal lobe vol (mm^3)	51848.0	7927.9	37105.8	71346.7
Right temporal lobe vol (mm^3)	69934.4	7795.8	49938.6	88618.3
Left temporal lobe vol (mm^3)	65973.1	7951.5	38473.5	86525.3
Right AHC volume (mm^3)	5063.5	702.2	3609.9	7122.6
Left AHC volume (mm^3)	4741.1	688.0	3010.8	6962.8

All scans were rated on various white matter lesion rating scales and visual ratings of atrophy (Appendix 9.6.3) but analyses in this thesis use only the Fazekas scale for white matter lesions (Fazekas et al., 1987). This has been well-validated and used in analyses of the Aberdeen 1921 birth cohort (e.g. Deary, Leaper, Murray, Staff, & Whalley, 2003b; Leaper et al., 2001). Descriptive statistics for this rating scale are presented in Table 3.10 (PVH median = 1, interquartile range 1, 2; DWMH median = 1, interquartile range 1, 1).

Table 3.10 Fazekas scale white matter lesion (WML) scores for 110 subjects

Scale	n	%
PVH 0	0	0
PVH 1	57	51.8
PVH 2	36	32.7
PVH 3	17	15.5
DWMH 0	8	7.3
DWMH 1	78	70.9
DWMH 2	17	15.5
DWMH 3	7	6.4

PVH = Periventricular hyperintensities
DWMH = Deep white matter hyperintensities

DTI results are presented in Table 3.11 for 105 people (1 excluded due to meningioma, 4 due to technical problems with DTI data). One female has no frontal measures and another no occipital measures due to inability to place a ROI in an area without visible white matter lesions.

Table 3.11 Diffusion tensor parameters in normal appearing white matter for 105 subjects (male n = 33)

	<D> (x 10^{-3} mm^2/s)					
	Male		**Female**		**Total**	
Brain region	**mean**	**SD**	**mean**	**SD**	**mean**	**SD**
Frontal	.854	.054	.833	.035	.840	.043
Occipital	.771	.045	.756	.031	.761	.037
Centrum semiovale	.784	.058	.761	.033	.768	.044
	Fractional anisotropy (FA)					
Frontal	.31	.03	.30	.03	.30	.03
Occipital	.42	.04	.42	.05	.42	.04
Centrum semiovale	.40	.06	.39	.06	.39	.06

4 Relationship between cognitive ability and structural brain indices

Brain imaging has played a major role in trying to understand the biological bases of cognitive change over the lifespan. This chapter presents data from the structural MRI scans performed in the Simpson's study to investigate the relationship between cognitive ability and the two major brain changes seen in cognitive ageing (see Chapter 1.1.1), namely atrophy and white matter lesions (WML).

4.1 Cognitive ability and brain volumes

4.1.1 Introduction

Studies of structural brain changes with age have shown a decrease in cortical volume (Chapter 1.1.2), with atrophy which is mostly confined to white matter, due to a decrease in myelinated fibres and an increase in extracellular space (Nusbaum et al., 2001). Cross-sectional studies in older people, focussing on disease states such as Alzheimer's disease, often report correlations between specific brain region volumes (such as the hippocampus) and specific cognitive domains (such as declarative memory) (Lupien, de Leon, De Santi, & et al., 1998). The implication is that this relationship is causal, with a decrease in the hippocampal size causing the impairment in memory. Relationships between brain volumes and cognitive function in older people are often interpreted as reflecting ageing-related atrophy, but they may also be due to an association between brain structure and cognitive ability that remains stable over the lifespan. Cognitive ability differences are quite stable from childhood into old age (Deary et al., 2000), and therefore impaired performance in later life may reflect long-standing lower ability rather than pathological decline (Chapter 1.1.1). Group mean performance on some tests stays relatively stable with age (crystallised ability, e.g. vocabulary) whereas performance on other tests tends to decline after mid-adulthood (fluid ability, e.g. problem solving). There is a consistently documented moderate correlation between brain size and cognitive ability in young adulthood (McDaniel, 2005), but little evidence whether this relationship persists into old age (Chapter 1.1.2.1).

Two studies report an association between head size and cognitive ability in older people (Reynolds et al., 1999; Tisserand et al., 2001). Although head size correlates with brain size these cannot be seen as equivalent, particularly in the elderly, in view of ageing related cerebral atrophy, and these studies did not account for prior cognitive ability. Neuroimaging allows in vivo measures of brain size to be made. The size of the skull vault remains stable throughout life and reflects the maximum size of the brain, attained by around age six (Gale et al., 2003). Maximal brain size can therefore be estimated by measuring intracranial skull volume in neuroimaging studies. Intracranial volume and thus maximal brain volume can be estimated reliably and validly by intracranial area (Appendix 9.6.1), which is a much less labour intensive method (Ferguson et al., 2005).

A meta-analysis of neuroimaging studies of brain volume and intelligence reviewed 24 studies in adults ($r = .41$ for females, $r = .38$ for males, .33 for sexes combined), but the mean age was not reported (McDaniel, 2005). One well-powered study of 97 unmedicated healthy elderly men (mean age 67.8 SD 1.3 years) found a positive association between brain size and cognitive ability (MacLullich et al., 2002). The relationships between specific cognitive tests and regional brain volumes were best summarized by a significant positive relationship between the latent traits of a general brain size factor and a general cognitive factor (structural equation modelling, correlation = .42) and not by associations between individual tests and particular brain regions. One further study of older people has not been published to date (ABC 1921), but the results included in a meta-analysis show no significant association between brain volume and cognitive ability in 106 subjects aged around 80 (McDaniel, 2005). Therefore, in healthy elderly men, the relationship between brain region volume and cognition may be largely due to longstanding associations between general cognitive ability and overall brain size, but there is a need for further studies.

The present study aimed to investigate the relationship between brain size and cognitive ability in the Simpson's study cohort. This differs from MacLullich et al's study because it is a more representative sample of community dwelling older people

(i.e. not specifically selected for good health), the participants are about 15 years older, and are mostly women. It also includes a measure of whole brain volume, rather than deriving a latent trait from regional brain volumes.

The two main issues to be investigated were 1) If an association between brain size and cognitive ability was confirmed in old age, was this a 'true' current association or would this be accounted for by a relationship between brain size and cognitive ability from earlier life? Prior brain size was estimated using the archaeological measure of intracranial area, and prior cognitive ability by estimating crystallised intelligence (Gc) using the National Adult Reading Test (NART). If the association between current ability and brain size was due to persistence of this association from earlier life, then the association between brain size and current ability (Gf) would be attenuated when corrected for prior ability (Gc). 2) If an association between brain size and cognitive ability was confirmed in this cohort, would any association be between specific cognitive domains and brain regions, or general cognitive ability (*g*) and overall brain size?

The hypotheses were that there would be an association between overall brain size and cognitive ability in older age, but that the association between fluid ability (Gf) and brain size would be attenuated by correcting for crystallised intelligence (Gc). The relationships among general and specific cognitive functions, particular brain regions, and whole brain volume were also investigated. The hypothesis was that the main association would be between *g* and whole brain volume, rather than specific tests and brain regions.

4.1.2 Methods

4.1.2.1 Imaging

The methods for recruitment and neuropsychological testing are presented in Chapter 2. The methodology for acquiring and analysing the MRI images in presented in Appendix 9.6.1 and 9.3.2 respectively. In brief, a standard structural brain MRI protocol was followed, comprising (1) sagittal T1-weighted spin-echo (2) axial T2-weighted fast spin-echo (FSE) (3) axial fluid attenuated inversion recovery (FLAIR) (4) axial T2* gradient echo , and (5) three-dimensional fast spoiled gradient echo T1

weighted volume sequence (inversion recovery prepared) with whole brain coverage. Semi-automated analysis was performed on the 3 directional 128-slice scan at 90° to hippocampus. The whole brain volume includes all brain tissue, with a limit imposed in a horizontal line across the bottom-most part of cerebellum as posterior limit. Intracranial area was measured in the midline sagittal slice of the sagittal localiser by manually tracing round the inner table of the cranial vault, along the superior surface of the floor of the frontal fossa and across the pituitary fossa to the dorsum sella. Tracing continued down the posterior surface of the clivus and completed by a line joining the anterior and posterior rims of the foramen magnum.

4.1.2.2 Statistical analysis

Sex differences between brain regional volumes were investigated using t-tests. Correlations among cognitive tests and brain volumes were investigated using Pearson's r (apart from MMSE which showed a ceiling effect, and was therefore analysed using Spearman's ρ). A measure of cerebral atrophy was provided by adjusting whole brain volume for intracranial area created by saving standardised residuals from a linear regression (whole brain volume was the dependent variable and intracranial area was the independent variable). Regional brain volumes were analysed uncorrected, and adjusted in turn for current and maximal brain volume, again created by saving standardised residuals from a linear regression (regional volume was the dependent variable and whole brain volume or intracranial area was the independent variable).

4.1.3 Results

Volumetric data were available for 107 of the 110 subjects who underwent MRI scan (exclusions for incidental findings of left frontal meningioma, pituitary adenoma and left temporal cyst). Descriptive results are presented for the cognitive test scores (Table 4.1), and the brain volumes (Table 4.2), of this 107 (compare with results for the full 110 with imaging performed in Chapter 3, Table 3.3).

These results show that this group is of generally higher mental ability than the general population, (mean NART of 29.9 equivalent to WAIS-R full scale IQ score of 106 (Nelson et al., 1991). They are, however, less able than a younger sample

selected to be healthy (e.g.(MacLullich et al., 2002) NART 36.2, SD 9.3; VF 43.4 SD 13.1; RSPM 41.5 SD 8.6).

Table 4.1 Cognitive test scores for 107 subjects with valid volumetric data

Test	n	Mean	SD
MMSE	104	28.4	1.4
NART (positive score)	107	29.9	7.9
RSPM	104	30.5	8.0
Moray House Test	101	57.1	8.7
Verbal fluency (total)	107	37.1	12.2
Logical Memory Total	106	33.1	11.6

MMSE = Mini-mental state examination
NART = National Adult Reading Test
RSPM = Raven's Standard Progressive Matrices

Table 4.2 Neuroimaging results (area and volumes) for 107 subjects with valid volumetric data

Variable	Mean	SD	Min	Max
Whole brain volume (cm^3)	1,135.5	984.3	947.4	1,405.2
Intracranial area (cm^2)	148.6	103.1	129.3	173.7
Corpus callosum area (mm^2)	540.0	83.5	392.0	775.2
Ventricular volume (mm^3)	30,549.4	18,893.7	4,655.7	96,263.5
Right frontal lobe vol (mm^3)	55,575.9	7,953.7	38,878.7	77,656.7
Left frontal lobe vol (mm^3)	51,705.4	7,985.1	37,105.8	71,346.7
Right temporal lobe vol (mm^3)	69,748.9	7,724.6	49,938.6	88,618.3
Left temporal lobe vol (mm^3)	66,068.8	7,480.1	52,574.8	86,525.3
Right AHC volume (mm^3)	5,056.2	706.0	3,609.9	7,122.6
Left AHC volume (mm^3)	4,753.6	671.4	3,088.4	6,962.8

These values are broadly comparable with other studies (MacLullich et al., 2002; Fotenos et al., 2005). Note these results are not subdivided by sex, but women have smaller volumes in all regions (t test P all <.001, except ventricular volume P = .04) except corpus callosum area P = .23. If brain volumes are corrected for BMI to assess

whether this is due to difference in body size the sex differences remain (P all <.001 except ventricular volume P = .06).

In view of the positive intercorrelations between the fluid-type cognitive tests (Table 4.3), data reduction was performed using principal components analysis to extract the first unrotated principal component. This general cognitive factor (*g*) explained 51.9% of the shared variance in these cognitive test scores (cases excluded listwise, therefore n for *g* = 99). The factor loadings were MHT .88, RSPM .83, verbal fluency .60, logical memory .50.

Table 4.3 Correlation coefficients among cognitive test scores (Pearson's r except MMSE, Spearman's ρ)

Test	MMSE	RSPM	MHT	VF	LM	*g*
RSPM	.18					
Moray House Test	**.35***	**.69***				
Verbal fluency	**.21***	**.25**	**.42***			
Logical Memory Total	.08	**.28***	**.25**	.11		
NART (positive score)	**.32***	**.30***	**.56***	**.43***	.17	**.52***

Bold type: P <.05 * P <.01

Correlations among measures of brain size are shown in Table 4.4.

Table 4.4 Correlations among brain volumes and intracranial area

	WBV	ICA	CCA	VV	RFL	LFL	RTL	LTL	RAHC
ICA	**.79***								
CCA	**.38***	**.31***							
VV	**.28***	**.42***	.02						
RFLV	**.59***	**.41***	-.01	**.21**					
LFLV	**.61***	**.41***	-.04	.18	**.67***				
RTLV	**.79***	**.59***	**.33***	.14	**.50***	**.40***			
LTLV	**.72***	**.49***	**.22**	-.03	**.30***	**.57***	**.77***		
RAHCV	**.53***	**.42***	.19	.12	**.30***	**.20**	**.63***	**.54***	
LAHCV	**.53***	**.38***	.05	.03	**.30***	**.27***	**.58***	**.65***	**.83***

Bold type: P <.05 * P <.01

ICA = intracranial area
WBV = whole brain volume
CCA = corpus callosum area
RFLV = right frontal lobe volume
LFLV = left frontal lobe volume
RTLV = right temporal lobe volume

VV = ventricular volume LTLV = left temporal lobe volume
RAHCV = right amygdalo-hippocampal complex volume
LAHCV = left amygdalo-hippocampal complex volume

Correlations among brain size indices and cognitive tests are shown in Table 4.5. The absolute values for regional volumes, rather than corrected for ICA or WBV, were used for analyses as we were interested in the possibility of associations between specific regional volumes and cognitive tests.

Table 4.5 Correlations among brain volumes, intracranial area and cognitive tests (Pearson's r except MMSE, Spearman's ρ)

	WBV	ICA	CCA	VV	RFL	LFL	RTL	LTL	RAHC	LAHC
MMSE	-.05	.03	.19	.13	-.11	-.13	-.08	-.04	.03	-.04
NART	.19	**.26***	.16	.19	.07	-.02	.14	.12	**.22**	**.24***
RSPM	**.28***	**.29***	.26	.08	.18	.05	**.30***	**.22**	.16	.15
MHT	**.26***	**.29***	.19	.08	**.23**	.07	**.30***	.19	**.20**	**.21**
VF	.13	.12	.14	-.07	.09	.02	.14	.13	**.19**	**.20**
LM	-.14	-.05	-.12	.07	-.03	-.11	-.13	-.16	-.05	-.04
g	**.24**	**.27***	**.21**	.09	.19	.05	**.26***	.18	.17	.18
***g* corr for NART**	.16	.16	.17	-.02	.16	.06	**.22**	.13	.09	.08

Bold type: P <.05 * P <.01

n varies from 104 to 107 depending on cognitive test (Table 6.1) and n = 99 for *g*

ICA = intracranial area
WBV = whole brain volume
CCA = corpus callosum area
VV = ventricular volume
RAHC = right amygdalo-hippocampal complex volume
LAHC = left amygdalo-hippocampal complex volume
RFLV = right frontal lobe volume
LFLV = left frontal lobe volume
RTLV = right temporal lobe volume
LTLV = left temporal lobe volume

MMSE = Mini-mental state examination
NART = National Adult Reading Test
RSPM = Raven's Standard Progressive Matrices
MHT = Moray House Test
VF = Verbal Fluency
LM = Logical Memory

Broadly, there is a positive association between whole brain volume and *g* (r = .24, P <.05). For specific cognitive tests there is a significant correlation between WBV and RSPM (r = .28, P <.01) and MHT (r = .26, P <.01), a trend for NART (r = .19) and verbal fluency (r = .13), no significant association for MMSE, and a non-significant

negative association for logical memory (r = -.14). The same pattern holds for the association between intracranial area (ICA) and individual cognitive tests.

To investigate whether lifelong brain shrinkage influenced cognitive ability in older life, brain shrinkage was estimated by correcting WBV for ICA (linear regression, WBV dependent variable, ICA independent variable, saving standardised residuals). There was no significant correlation between brain atrophy and cognitive function (except for logical memory where the negative association persists) (Table 4.6). Particularly, the association between WBV and MHT is attenuated from r = .26 to .06. The percentage variance attenuated by correcting for ICA is considerable, e.g. for MHT, correcting for ICA attenuates the variance explained by 94.7%, and for *g* by 96.6%. Thus, the association between brain size and cognitive ability in older life is due to the association between ability and maximal brain size. In stepwise linear regression, ICA accounted for 6.2% of the variance in *g* (β = .27, P = .007), but no additional variance was explained by brain shrinkage (WBV corrected for ICA).

Table 4.6 Correlations between WBV (raw and corrected for ICA) and cognitive tests (Pearson's r); and percentage variance attenuated by correcting WBV for ICA (n = 107)

	WBV	WBV corrected for ICA	% variance attenuated
MMSE	-.05	-.00	-
NART	.19	.01	99.7
RSPM	**.28***	.13	78.2
MHT	**.26***	.06	94.7
VF	.13	.08	62.4
LM	-.14	**-.23**	-
g	**.24**	.05	96.6
***g* corr for NART**	.16	.05	90.4

Bold type: P <.05 * P <.01

MMSE = Mini-mental state examination
NART = National Adult Reading Test
RSPM = Raven's Standard Progressive Matrices
MHT = Moray House Test
VF = Verbal fluency
LM = Logical Memory

These correlations were repeated as partial correlations correcting for sex, and the correlation coefficients were slightly attenuated, but the same pattern was seen.

In addition to the correlations between whole brain volume and cognitive ability described above, there are associations between specific brain regions and specific cognitive tests (Table 4.5), e.g. an estimate of prior IQ (NART) and AHC; RSPM, a test of non-verbal fluid intelligence, and temporal lobes; Moray House Test, a test of verbal reasoning, and frontal and temporal lobes on the right side only, and AHC bilaterally; Verbal fluency (a test of executive function) with AHC bilaterally (and not with frontal lobes).
Logical memory correlates negatively (though non-significantly) with all regional and whole brain volumes.
The general cognitive factor *g* correlated with whole brain volume and intracranial area, but no regional volume except right temporal lobe. If *g* corrected for NART is used as an estimate of cognitive change, these associations are attenuated to non-significant levels, except for right temporal lobe ($r = .22$, $P < .05$) (Table 4.5).

When these correlations were repeated using regional volumes corrected for intracranial area or whole brain volume (using standardised residuals) none reached statistical significance, i.e. the main association is between overall brain size and cognitive ability, rather than any specific region.

4.1.4 Discussion

In this study of community dwelling men and women aged around 80 there is a small to moderate positive association between a general cognitive factor (*g*) and whole brain volume (WBV). However, there is also a small to moderate positive association between the general cognitive factor and intracranial area (ICA), an estimate of maximal brain size (achieved by age six). When WBV was corrected for ICA (a measure of brain atrophy) the effect size of the correlation with current cognitive ability was attenuated and became non-significant (r decreasing from .24 to .05 i.e. the shared variance decreased by 96.6%). Also, when old age cognitive ability was corrected for estimated prior ability, the association was attenuated from $r = .24$ to .16 (a reduction in shared variance of 33.3%) and became non-significant. This

suggests that the association between WBV and cognitive ability in older age is largely due to the persistence of this association from earlier life, as shown by the association between NART and ICA (r = .26). There were associations between regional brain volumes and specific cognitive tests, but these associations all became non-significant when corrected for brain size. Therefore associations between brain regions and specific cognitive abilities may be largely due to the underlying life-long association between general cognitive ability and overall brain size.

This sample is well-placed to investigate the relationship between cognitive ability and brain volumes. The participants are well-characterised, and all had a standard test battery performed by one administrator. The estimate of childhood IQ using the NART was validated against an actual age 11 measure in 31 of the sample (r = .73). Volumetric analyses were performed blind to all other data.

These results replicate the finding of an association between brain size and cognitive ability which is well-recognised in younger samples (McDaniel, 2005; Andreasen et al., 1993), and was found in a group of somewhat younger, healthy men (MacLullich et al., 2002). However, in addition to the association between brain size and cognitive ability, there was an association between internal head size (intracranial area) and cognitive ability. This suggests that the brain size-cognition relationship has persisted throughout life. That is, the correlation between current ability and current brain size in old people is largely accounted for by associations between 'archaeological' ability (NART) and brain size (intracranial area). Studies in older age have suggested that this relationship is consistent with the 'brain reserve hypothesis' (Satz, 1993; Stern, Silva, Chaisson, & Evans, 1996), that individuals with larger brains are better placed to withstand pathological processes before exhibiting cognitive decline (Tisserand et al., 2001). Brain reserve comprises more than merely brain size, however, (e.g. the complexity of neural connections) and intellectual challenges accumulated throughout life, such as education and occupational attainment, are likely to be more important for maintaining cognitive abilities (Stern, 2003; Staff, Murray, Deary, & Whalley, 2004).

From a life course perspective, small brain size can be seen as an associate of low birth weight, and poorer cognitive performance may in fact reflect changes programmed in utero (Chapter 1.2.1). However, the studies discussed in Chapter 1.2.1 (Gale et al., 2004; Gale et al., 2003; Martyn et al., 1996) suggest that the association between head size and cognitive ability is determined postnatally, and is independent of sex, parity, maternal IQ, age, education, social class, duration of breastfeeding and history of post-partum low mood. Future studies should examine influences during infancy and early childhood to investigate whether there are any potential targets for intervention to improve cognitive ability in childhood, and thus throughout adult life. However, it should be noted that the effect size is small: ICA accounts for only around 6% of the variance in *g*.

Studies of cognitive ageing correlating brain regional volume with psychometric tests often adjust regional volumes for brain size (Lye et al., 2004; Callen, Black, Gao, Caldwell, & Szalai, 2001; Du et al., 2001). Our study suggests that this may mask an important association. In this relatively large dataset, correcting for ICA eliminated all of the statistically significant associations between regional and overall brain volume and cognitive ability. Although in studies of diseases such as dementia correcting for prior brain size may still reveal associations between profound atrophy and marked cognitive decline (Callen et al., 2001; Du et al., 2001), studies of normal cognitive ageing or mild cognitive impairment are likely to have more subtle changes. Individual differences in performance in normal ageing are more strongly related to prior ability, and its association with brain size, than as a consequence of brain atrophy.

The main result in this study is that the association between an estimate of childhood ability (NART) and maximal brain size (ICA) accounts for the association between cognitive ability and brain size in older age. This emphasises the importance of a life course perspective when examining older people: prior cognitive abilities and brain size are important to consider when investigating cognitive ageing.

4.2 Cognitive ability and White Matter Lesions

4.2.1 Introduction

The two main structural brain changes associated with ageing are volume loss (as discussed above in Chapter 1.1.2.1 and 4.1) and the accumulation of white matter lesions (WML). White matter lesions (or abnormalities or hyperintensities) are areas of high signal on T2 and proton density weighted images, and are commonly separated into patchy deep white matter hyperintensities (DWMH) and smooth periventricular hyperintensities (PVH) (See Chapter 1.1.2.2 and Figure 1.2). Most MRI visual rating scales distinguish between these (Scheltens et al., 1998), and they are thought to have different aetiologies and functional consequences (Schmidt et al., 2004), but see (DeCarli et al., 2005a). In general, however, all WML probably have an ischaemic aetiology, (Pantoni & Garcia, 1997; DeCarli et al., 2005a), possibly via breakdown of the blood-brain barrier (Wardlaw et al., 2003).

The prevalence of WML increases with age, (Longstreth, Jr. et al., 1996) and their presence has been associated with many ageing-related conditions e.g. impaired balance and gait, (Breteler et al., 1994; Starr et al., 2003) depression, hypertension (Fazekas et al., 1987), transient ischaemic attack or stroke (Longstreth, Jr. et al., 1996; Vermeer et al., 2003b) and reduced respiratory function (Liao et al., 1999). The evidence for an association between WML and cognitive ageing was initially unconvincing, with early studies, often including participants with and without Alzheimer's disease, showing no association between WML and cognitive decline (Leys et al., 1990; Starkstein et al., 1997). More recently, however, a consensus has emerged that there is a decline in cognitive abilities with increasing WML, and people with WML have an increased risk of dementia (Vermeer et al., 2003b). There is still debate as to the cognitive domains affected, and the importance of the site of WML (see Chapter 1.1.2.2). A meta-analysis found most evidence for an association between WML and processing speed, memory, and indices of global cognitive function (Gunning-Dixon et al., 2000; de Groot et al., 2000).

In a study of survivors of the Scottish Mental Survey 1932 in Aberdeen (Aberdeen Birth Cohort 1921) 95 subjects underwent brain MRI and cognitive testing (Leaper et al., 2001). They found an association between WML load and tests of fluid intelligence (Raven's Progressive Matrices, Digit Symbol, Block Design, Uses for Common Objects) but not crystallised intelligence (NART, Moray House Test age 11). The associations were stronger for DWMH ($r \sim .25$-$.33$) than PVH ($r \sim .16$-$.26$). A further study of this cohort used structural equation modelling to show that WML (irrespective of location) and childhood mental (crystallised) ability contributed independently to the variance in general cognitive (fluid) ability at age 78 years (Deary et al., 2003a). This study also suggested that hypertension might partly account for the effect of WML on cognition, and also have a small direct effect. There was no contribution to any specific cognitive test.

As this sample was very similar to the ABC 1921 cohort, with similar data, the primary hypothesis was that there would be an association between WML and tests of fluid ability (Gf), but no association with crystallised ability (Gc). Based on the meta-analysis (Gunning-Dixon et al., 2000) the secondary hypothesis was that, for individual tests, the strongest associations would be for verbal fluency, MMSE and logical memory, but not RSPM or MHT.

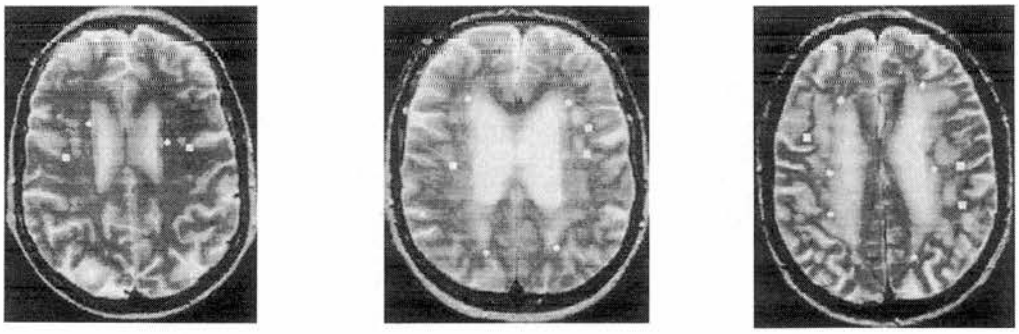
4.2.2 Methods

4.2.2.1 Imaging

The methods for recruitment and neuropsychological testing are presented in Chapter 2. The methodology for acquiring and analysing the MRI images for WML is presented in Appendices 9.6 and 9.7 respectively. In brief, a standard structural brain MRI protocol was followed, comprising (1) sagittal T1-weighted spin-echo (2) axial T2-weighted fast spin-echo (FSE) (3) axial fluid attenuated inversion recovery (FLAIR) (4) axial T2* gradient echo , and (5) three-dimensional fast spoiled gradient echo T1 weighted volume sequence (inversion recovery prepared) with whole brain coverage. The T2-weighted MRI images were analysed by an experienced neuroradiologist (Professor J Wardlaw) blind to all other data. Several rating scales were used (Appendix 9.6.3), but the Fazekas scale (Fazekas et al., 1987) has proved

to be the most reliable, and will be presented here. This rates DWMH and PVH separately on a four point scale (0-3) (Figure 4.2).

Figure 4.2 Scoring of WML on Fazekas scale (from Leaper et al, 2001)



Grade 1	Grade 2	Grade 3
Deep white matter hyperintensities □		
Punctuate focal lesions	Some confluence	Large confluent areas
Periventricular hyperintensities O		
Pencil thin lining	Smooth halo	Irregular extension

4.2.2.2 Statistical methods

Associations between WML load score and cognitive test result were performed using non-parametric correlations (Spearman's ρ). In view of the inability to perform partial correlations correcting for age when using Spearman's ρ, cognitive test scores were corrected for age (at cognitive test) using standardised residuals from a linear regression (test score was the dependent variable and age at test was the independent variable).

Principal components analysis was used to extract a general cognitive factor (*g*) from the tests of more fluid ability. This general cognitive factor (*g*) explained 51.3% of the shared variance in these cognitive test scores (cases excluded listwise, therefore n for $g = 102$). The factor loadings were MHT .89, RSPM .82, verbal fluency .61, logical memory .47. A measure of cognitive change was also included, by regressing *g* on NART and saving the residuals.

4.2.3 Results

Descriptive statistics for the cognitive tests and WML ratings for 110 people who underwent brain MRI are presented in Chapter 3.2 (Table 3.3) and Chapter 3.6 (Table 3.10). For DWMH range 0-3; median 1; interquartile range 1, 1; for PVH 1-3; 1; 1, 2. The incidental structural findings (meningioma, temporal cyst, pituitary adenoma) did not interfere with coding for WML, and all cases are included in these analyses.

Correlations between WML and cognitive test score (raw and corrected for age) are presented in Table 4.7.

Table 4.7 Correlations among cognitive tests (corrected for age) and WML (Spearman's ρ) in 110 subjects

	n	DWMH		PVH	
		Raw	Corr for age	Raw	Corr for age
Hypothesis		Negative	Negative	Negative	Negative
g	102	-.02	.00	-.10	-.07
MMSE	107	-.10	-.09	**-.21**	**-.19**
RSPM	107	-.06	-.05	-.13	-.11
MHT	104	.02	.04	-.13	-.10
VF	110	-.02	.01	-.10	-.06
LM	109	-.04	-.01	-.02	.00
***g* corrected for NART**	102	.04	.05	-.08	-.06
NART Hypothesis		None	None	None	None
NART	110	-.03	-.01	-.00	.00

Bold type: P <.05

MMSE = Mini-mental state examination
NART = National Adult Reading Test
RSPM = Raven's Standard Progressive Matrices
MHT = Moray House Test
VF = Verbal fluency
LM = Logical Memory

This shows a weak and statistically non-significant negative association between PVH and *g*. Increased PVH is associated with poorer score on MMSE. There are also weak negative associations between PVH and RSPM, MHT and verbal fluency.

There is no significant association with logical memory. There is no significant association between WML and NART (test of crystallised ability).

To ensure these results were not an artefact of the particular WML rating scale used the analyses were repeated using all the WML scales (Appendix 9.6.3), and a similar pattern was seen, i.e. a small, non-significant, negative correlation between cognitive test score and WML score (Table 4.8).

Table 4.8: Correlations among cognitive tests (corrected for age) and WML rating according to various scales (Spearman's ρ) for 110 subjects

	Wahlund	**Longsteth**	**van Swieten**		**Breteler**	**Shimada**	**Mirsen**	**Wahlund ARWMC**
	PVH & DWMH	PVH & DWMH	Ant WML	Post WML	PVH	PVH	DWMH	DWMH & BG
g	.01	-.06	-.07	-.00	-.01	-.12	-.05	-.07
MMSE	-.02	-.15	-.07	-.00	.04	-.15	-.04	-.02
RSPM	-.09	-.13	-.11	-.03	-.11	-.18	-.12	-.10
MHT	.03	-.02	-.05	.06	.04	-.02	-.01	-.07
VF	.06	-.04	-.02	-.04	.07	-.06	.09	-.04
LM	.04	-.03	-.01	-.06	.04	-.06	-.04	-.01
***g* corr for NART**	-.10	-.14	-.09	-.03	-.13	-.18	-.14	-.08
NART	.05	.05	.00	.10	.12	.03	.08	-.04

ARWMC = Age-related white matter change
PVH = Periventricular hyperintensities
DWMH = Deep white matter hyperintensities
WML = White matter lesions
BG = basal ganglia

MMSE = Mini-mental state examination
NART = National Adult Reading Test
RSPM = Raven's Standard Progressive Matrices
MHT = Moray House Test
VF = Verbal fluency
LM = Logical Memory

This shows that for all scoring systems there is generally a negative correlation between cognitive test score and WML load, although none of these reach conventional levels of statistical significance. Interestingly, the association with NART is generally positive (i.e. those who had a higher estimated early-life cognitive ability had more WML), and this was checked by correlating the actual age 11 cognitive test score (n = 31) with WML ratings. These correlations were also

positive (ρ .03 to .33), although none reached conventional statistical significance. Thus, there was no significant association between crystallised/prior intelligence and WML load, and perhaps a suggestion that subjects with increased WML load may have performed better as children.

4.2.4 Discussion

There was a trend towards an association between WML and cognitive ability in old age, but this was only statistically significant for PVH and a test of global cognitive ability (MMSE). There was no association between WML and crystallised ability (NART; and indeed a suggestion that the relationship was positive). Associations were generally stronger for PVH than DWMH.

A general cognitive factor is commonly used in psychometric research as it accounts for 40-50% of the variance in any mental test battery (Spearman, 1904; Deary, 2000b). In cognitive ageing, much of the effect of age on cognitive ability is on the general factor, with relatively little effect on specific cognitive functions (Salthouse, 2000). However, contrary to our hypothesis, in this study there was no significant effect of DWMH or PVH on *g*. This may be because the strongest factor loadings were from tests of verbal and non-verbal ability (MHT and RSPM). MMSE, as a crude screening test for global cognitive ability, was not included in the principal components analysis. It is, however, commonly used both in clinical practice and cognitive research. We found a significant association between PVH and MMSE, despite its limited range (24 to 30 in this cohort). Therefore, although the association PVH and MMSE may be due to chance in this cohort, MMSE should be included in studies of normal cognitive ageing.

Contrary to our hypotheses, there was no significant association between WML and verbal fluency (a test of executive function) or memory. There was a trend towards a negative association for MHT and RSPM. The difference between this and previous studies may be due to chance (a type I error), the choice of different cognitive tests, or specific characteristics of this cohort, in particular other factors influencing cognitive performance not accounted for in analyses, and therefore confounding the results. This cohort is a volunteer group from the community, but was not selected to

be representative of the community. They are relatively healthy (compared to their peers) and more cognitively able. They are however, more representative of 'typical' older people in the community than subjects recruited to studies while attending hospital for investigation of cognitive decline. There is a need for a comprehensive meta-analysis including recent trials and unpublished studies to assess the influence of WML on cognitive function.

As hypothesised there was no association between WML and crystallised ability (NART), in line with previous studies (Deary et al., 2003b; Leaper et al., 2001). WML therefore contributes to cognitive decline independent of prior ability (Deary et al., 2003b; Garde, Mortensen, Krabbe, Rostrup, & Larsson, 2000).

The effect size of the correlations was smaller than that found in previous studies. For example, in the Aberdeen 1921 cohort (Leaper et al., 2001), correlations were -.18 to -.33, and in the meta-analysis estimate of pooled effect size was -.2 (Gunning-Dixon et al., 2000). Reasons for this might include (1) the restricted range of the scoring system for WML. In the Aberdeen study three separate ratings of WML were made and the mean calculated, providing a continuous distribution of scores, unlike the three point scale used here. However, WML loads were similar between that and the Simpson's cohort (mean DWMH 1.13, SD .70 in Aberdeen; 1.22, SD .66 in the Simpson's study; mean PVH 1.27, SD .67; 1.64, SD .74 in the Simpson's study); (2) if the cohort were unusual, particularly with a restricted range of cognitive tests, or extreme outliers, but the descriptive statistics do not show that this cohort is unusual when compared to other community dwelling older volunteers.

The finding that the association between cognitive ability and WML was slightly stronger for PVH than DWMH, based on the slightly higher correlation coefficient, but there is no statistically significant difference between the two correlation coefficients. This interpretation should be treated with caution, but is consistent with previous studies (de Groot et al., 2001; Ylikoski et al., 1993). However, a recent study using 3D mapping techniques has suggested that the distinction between PVH and DWMH is arbitrary, due to the qualitative nature of the rating scales (DeCarli et

al., 2005a). They suggest that the relationship between cognitive ability and PVH may reflect total WML burden, with DMWH and PVH actually being contiguous, and due to a single vascular watershed area 3-13 mm from the ventricular surface. Future studies should assess WML in both qualitative and quantitative ways until the pathophysiology and functional consequences of WML (whether PVH or DWMH) are established.

In this chapter the data for brain size and WML have been presented separately, consistent with the vast majority of the literature. However, it is likely that the various structural brain changes that occur both in normal and pathological ageing interact to affect cognition. Some studies have attempted to account for both, e.g. correcting for brain size by dividing (log) white matter volume by total brain volume (Firbank et al., 2003). One research group has coined the term "Subclinical Structural Brain Disease" (SSBD) to encompass cortical atrophy, central atrophy, DWMH and PVH (Cook et al., 2002), finding that increased SSBD was associated with poorer cognitive function in healthy older people.

5 Relationship between cognitive ability and DTI parameters

5.1 Introduction

Chapter 1.1 describes how cognitive abilities change with age, but that the biological bases of these changes are not well understood (Deary et al., 2004b; Hedden et al., 2004). White matter lesions (WML) increase in prevalence with age, and may have a vascular aetiology (Schmidt et al., 2004). Increased WML load correlates with cognitive impairment (Deary et al., 2003b; de Groot et al., 2000), but studies disagree as to the size of the effect and the cognitive domains involved (Gunning-Dixon et al., 2000). This may be due to differences in study design, the multi-factorial aetiology of WML, and difficulty in coding WML, particularly the possible insensitivity of WML rating scales to subtle early pathology (Gunning-Dixon et al., 2000). Since disruption of white matter tracts connecting cortical regions may underlie cognitive decline (Geschwind, 1965; O'Sullivan et al., 2001a) there is a need for more sensitive measures of white matter integrity. This is particularly important if subtle changes are to be detected early in the disease process when it is more likely that interventions to slow or halt cognitive decline would be effective.

One such technique is diffusion tensor MRI (DTI), (described in Chapter 1.1.3) which provides a non-invasive method of investigating the ultra-structure of the brain, and may be sensitive to age-related white matter deterioration (O'Sullivan et al., 2001a; Sullivan et al., 2003). To recap, using this modality, the diffusion of water molecules *in vivo* can be characterised by two parameters, namely mean diffusivity (<D>), which measures the magnitude of water diffusion, and fractional anisotropy (FA), which indicates the directional coherence of diffusion predominantly in the extracellular space (Basser et al., 1996; Pierpaoli et al., 1996). The presence of axonal membranes and myelin means that water molecules diffuse preferentially in parallel with the long axes of tightly packed axonal bundles, rather than across them (Pierpaoli et al., 1996). These diffusion parameters are therefore thought to provide useful markers of white matter fibre bundle integrity, with low values of <D> and high values of FA indicating intact healthy neurons.

Several studies have found that <D> increases and FA decreases with age (Abe et al., 2002; Chen et al., 2001; Chun et al., 2000; Nusbaum et al., 2001; Head et al., 2004; Pfefferbaum et al., 2003)(Chapter 1.1.3.1). These changes occur in normal ageing, in parallel with changes in cognition, and therefore provide a plausible biological explanation for cognitive ageing (Deary et al., 2004b; Hedden et al., 2004). Five studies have explicitly examined the relationship between cognitive ability and DTI data in older people without clinical disease, providing most evidence for a relationship between DTI parameters in frontal regions and executive function (O'Sullivan et al., 2001a; Madden et al., 2004; Shenkin et al., 2003; Stebbins et al., 2001b; Moseley et al., 2002) (Chapter 1.1.3.2). However, these studies all have small numbers of subjects (17 to 31) and large age ranges (*e.g.* 19 to 70 (Madden et al., 2004) and 56 to 85 years (O'Sullivan et al., 2001a)). There is therefore a need for more adequately powered studies with subjects of narrow age-range to investigate further whether reduced white matter integrity is one of the foundations of individual differences in cognitive ageing.

In this study, the relationships between cognitive ability and both WML load and DTI parameters in a large cohort of community dwelling older people with a narrow age range were investigated. WML scales were used to score lesions visible on structural MRI scans, while DTI parameters were measured in normal-appearing white matter to characterize more subtle changes in white matter integrity. It was hypothesised that WML load and DTI parameters have associations with cognition, with higher WML score and increased <D> and decreased FA correlating with worse cognitive function. Furthermore, based on the results of previous smaller studies, it was hypothesised that relationships between DTI parameters and cognitive ability are strongest in frontal regions, and with tests of executive function.

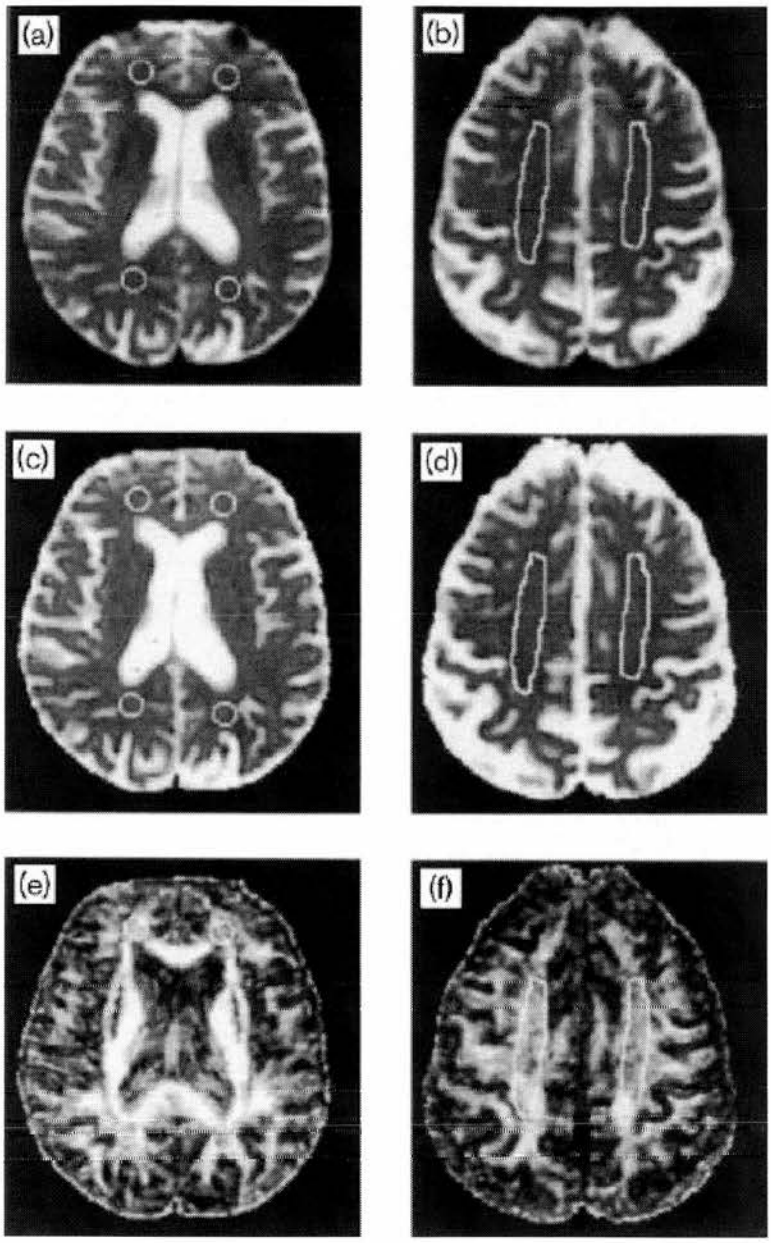
5.2 Methods

5.2.1 Imaging

The methodology used for collecting the clinical and neuropsychological data is presented in Chapter 2.5 and 2.6, and the DTI methodology in Appendix 9.7. Briefly, all subjects who completed the MRI scan (approx 40 minutes) included

data acquisition for DTI based on spin-echo echo-planar (EP) imaging (Shenkin et al., 2003). The duration of the examination was approximately 40 minutes. Sets of axial EP images (b = 0 and 1000 s/mm^2) were collected with diffusion gradients applied sequentially along six non-collinear directions. Five acquisitions consisting of a baseline T_2-weighted EP image and six diffusion-weighted EP images, a total of 35 EP images, were collected per slice position. From the DTI data, the apparent diffusion tensor of water (**D**) was calculated in each voxel from the signal intensities in the component EP images (Basser et al., 1996). Maps of <D> and FA for each subject were generated on a voxel-by-voxel basis from the sorted eigenvalues of **D** and converted into Analyze (Mayo Foundation, Rochester, MN, USA) format. Regions-of-interest (ROI) were placed in frontal and occipital white matter and centrum semiovale using the T_2-weighted EP images, avoiding areas with white matter lesions, following an approach adapted from O'Sullivan *et al* (O'Sullivan et al., 2001a) and described previously (Shenkin et al., 2003) (Figure 5.1). In this method, values of <D> and FA for normal-appearing frontal and occipital periventricular white matter were obtained from multiple small circular (69 voxels, volume 303 mm^3) ROI placed near the anterior and posterior horns of the lateral ventricles. Several larger, oval ROI (typically 500 voxels, volume 2197 mm^3) were also placed in normal-appearing centrum semiovale. Partial volume effects were minimised by siting the ROI at least 3 voxels from both the edge of the ventricles and abnormally appearing white matter. Since the T_2-weighted EP images and the DTI parametric maps were by definition co-registered, this allowed <D> and FA values to be measured simultaneously in the ROI. Mean <D> and FA values were obtained from the average of the left and right ROI measurements made in at least two appropriate slices for each region in every subject. The observer (TJM) was blind to the clinical status and cognitive function of participants, and purpose of the study.

Figure 5.1: Maps of T2 weighted signal intensity (a,b), <D> (c,d) and FA (e,f) obtained at the level of the lateral ventricles and centrum semiovale in an 80 year old female subject, showing typical location of ROI in frontal, occipital and centrum semiovale normal appearing white matter.



5.2.2 Statistical analyses.

Differences in DTI parameters between frontal and occipital white matter, and centrum semiovale were tested using repeated measures general linear modelling (one-factor within subjects ANOVA), and where differences were found these were investigated using Bonferroni adjusted pairwise comparisons. Bivariate correlations were used to investigate the relationship between: (i) DTI parameters and age (Pearson's r), (ii) WML and age (Spearman's ρ), (iii) DTI parameters and WML load (Spearman's ρ), (iv) cognitive ability and WML load (Spearman's ρ), (v) cognitive ability and DTI parameters (Pearson's r), and (vi) whole brain volume and DTI parameters (Pearson's r). The influence of potential confounders on the relationship between cognitive ability and DTI was investigated using partial correlation. Sex differences in DTI parameters were tested using Student's *t*-test, and in WML using Mann-Whitney U test. Analysis of covariance was used to test whether both age and sex influenced <D>. The importance of a history of vascular risk factors on DTI parameters was tested using one-way ANOVA. All analyses were performed using SPSS version 12 (SPSS Inc, Chicago, Ill, USA).

Data reduction

As previously described in Chapter 3.2, principal components analysis was used to derive a general cognitive factor (*g*) from the tests of more fluid ability (Verbal fluency, Raven's SPM, Moray House Test, Logical Memory), which were positively intercorrelated (r from 0.08 to 0.66). In these 105 subjects, the first unrotated principal component accounted for 50.7% of the total variance. Each subject was given a score on this general cognitive factor (*g*), in addition to NART and MMSE scores. Correlations between brain MRI parameters and these scores were examined initially, and then the associations with individual test scores were calculated.

To investigate the influence of vascular risk factors, the cognitive test scores and DTI parameters of those with and without a history of vascular risk factors were compared using multifactorial ANOVA.

5.3 Results

General findings. Of the 115 subjects recruited, 105 had usable DTI data (see Chapter 3.6). 72 (68.6%) were female, and mean age was 78.4 (SD 1.5, range 75.5 to 81.5) years. There were no frontal measures for one participant, and no occipital measures for another (both female), due to inability to place an appropriate ROI. Vascular risk factors and whole brain volume are described in Table 5.1.

Table 5.1: Descriptive statistics for vascular risk factors and brain volume in 105 subjects

	n	%		
History of hypertension	48	45.7		
History of CaVD	35	33.3		
History of stroke / TIA	10	9.5		
History of NIDDM	6	5.7		
Current smoker	8	7.6		
Ex-smoker	49	46.7		
Carotid artery stenosis >60%				
Right	7	6.7		
Left	6	5.7		
MRI: infarct	8	7.7		
MRI: lacunar infarct	2	1.9		
	Mean	**SD**	**Min**	**Max**
Systolic BP (mmHg)	159.1	26.2	103	238
Diastolic BP (mmHg)	79.2	12.8	54	124
BMI (kg/m^2)	27.3	4.0	18.7	40.8
Whole brain volume (cm^3)	1136.5	98.6	947.4	1405.3

CaVD = cardiovascular disease (angina or myocardial infarct)
TIA = transient ischaemic attack NIDDM = non-insulin dependent diabetes
BMI = body mass index BP = blood pressure

Descriptive results - WML. Rating on the Fazekas scale was positively skewed for both PVH (range 1-3, median 1) and DWMH (range 0-3, median 1) (see Chapter 3.6 and Table 3.10). There was no significant sex difference in WML score, and no significant increase in WML scores with age.

Descriptive results - DTI. Table 5.2 (and 3.11) show <D> and FA for frontal, occipital and centrum semiovale regions.

Table 5.2: DTI parameters in normal appearing white matter in 105 subjects (male n = 33)

	<D> (x 10^{-3} mm^2/s)					
	Male		Female		Total	
Brain region	**mean**	**SD**	**mean**	**SD**	**mean**	**SD**
Frontal	.854	.054	.833	.035	.840	.043
Occipital	.771	.045	.756	.031	.761	.037
Centrum semiovale	.784	.058	.761	.033	.768	.044
	Fractional anisotropy (FA)					
Frontal	.31	.03	.30	.03	.30	.03
Occipital	.42	.04	.42	.05	.42	.04
Centrum semiovale	.40	.06	.39	.06	.39	.06

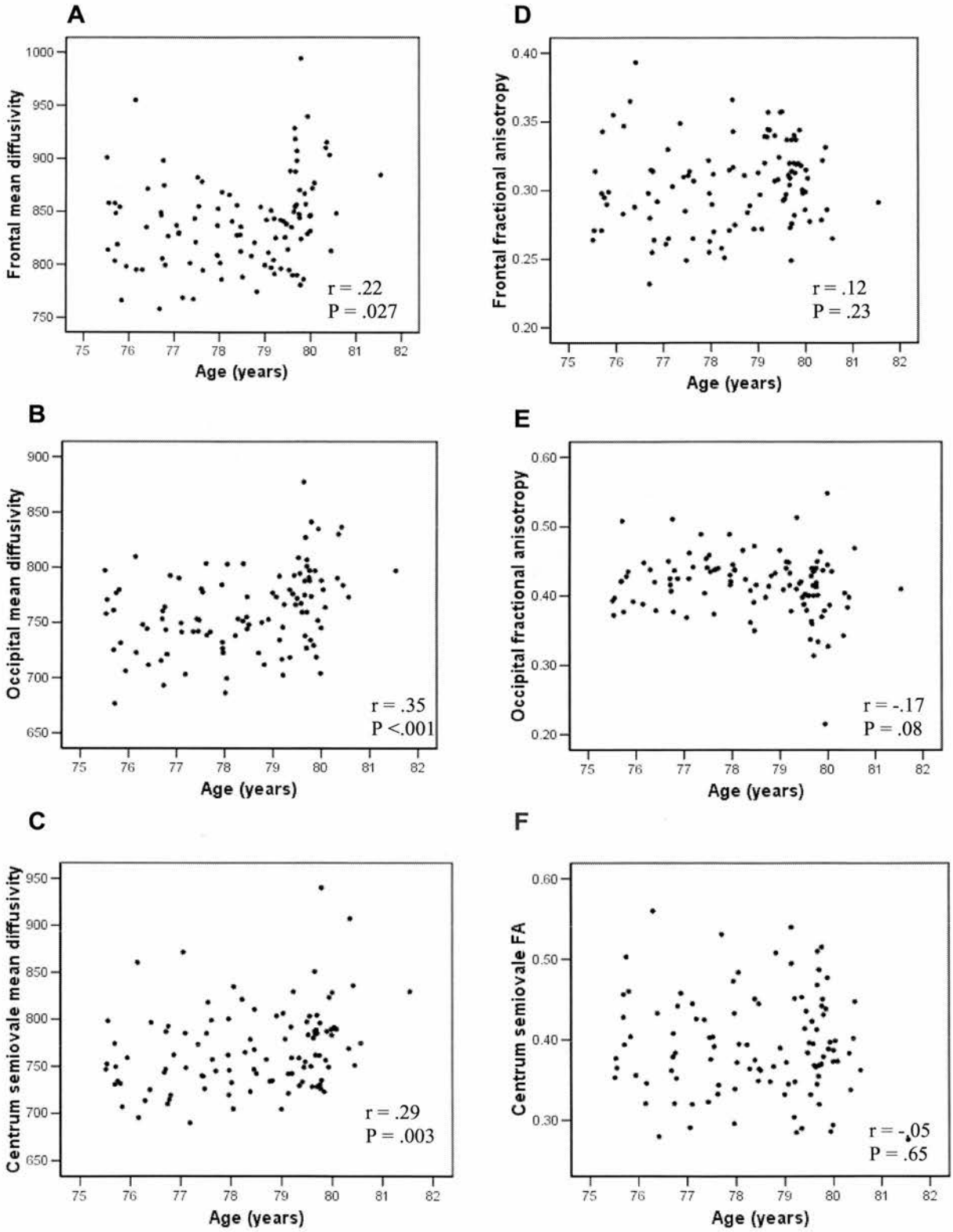
DTI: Regional differences: There were statistically significant differences between the regions for <D> ($F_{(2,204)}$ = 286.0; P <.001) and FA ($F_{(2,204)}$ = 178.8; P <.001). Bonferroni adjusted pairwise comparisons showed that the differences in <D> were between frontal and occipital (mean difference 78.6 x 10^{-3} mm^2/s, 95% CI 69.7 to 87.5, P <.001) frontal and centrum (mean difference 71.7 x 10^{-3} mm^2/s ,95% CI 63.7 to 79.7, P <.001, but not between occipital and centrum (mean difference 6.9 x 10^{-3} mm^2/s , 95% CI -2.7 to 16.5, P = .25). For FA there were significant differences between all areas: frontal and occipital (mean difference .11, 95% CI .10 to .12, P < .001) frontal and centrum (mean difference .09 95% CI .07 to .10, P < .001), occipital and centrum (mean difference .02 95% CI .01 to .04, P = .02) i.e. the frontal ROI had the highest <D> and the lowest FA.

Across all subjects, and correcting for age, <D> and FA were significantly negatively correlated in all three regions (frontal white matter: r == -.20, P < .05; occipital r = -.051, P <.001; centrum r = -.38, P <.001).

DTI and WML. Higher scores on WML load were associated with higher <D> in frontal white matter (ρ_{PVH} = 0.31, P <0.01; ρ_{DWMH} = 0.29, P <0.01) and centrum semiovale (ρ_{PVH} = 0.35, P <0.01; ρ_{DWMH} = 0.26, P <0.01) regions, but not occipital white matter (ρ_{PVH} = .10, P = .32; ρ_{DWMH} = .15, P = .13) or FA in any region (ρ all <.15).

DTI and Age. There was a significant association between age and <D> in all regions (frontal r = .22, P = .027; occipital r = .35, P <.001; centrum semiovale r = .29, P = .003), but no significant association between age and FA (frontal r = .12, P = .23; occipital r = -.17, P = .08; centrum semiovale r = -.05, P = .65) (Scatterplots are shown in Figure 5.2). Similar results were obtained using the Spearman non-parametric test (<D> frontal ρ = .25, occipital ρ = .27, centrum ρ = .30; FA frontal ρ = .12, occipital ρ = -.18, centrum ρ = -.16).

Figure 5.2 Scatterplots of age and DTI parameters
A) Frontal <D> B) Occipital <D> C) Centrum semiovale <D>
D) Frontal FA E) Occipital FA F) Centrum semiovale FA



DTI and Sex. Men had higher <D> than women, (frontal t = 2.08, P = .04, occipital t = 1.73, P = .09, centrum t = 2.08 P = .04; FA all P >.5), but there were no significant sex differences for FA. Men were significantly older than the women (t = 2.44; P = .02). Analysis of covariance was used to test the effects of age and sex on DTI. With both age and sex in the model, only age contributed to the variance in <D>, i.e. there was no sex difference in <D> when age was taken into account. There was no statistically significant interaction between age and sex.

Descriptive results - Cognitive tests. Results for the cognitive tests are shown in Table 5.3. Missing data was due to deafness, visual impairment, or tests not completed. The cognitive tests have a normal distribution, except for MMSE, which shows a ceiling effect.

Table 5.3: Descriptive statistics for cognitive test score results in 105 subjects with DTI data

Test	n	Mean	SD	Min	Max	Max possible
NART (positive score)	105	30.1	7.8	11	44	50
MMSE	102	28.3	1.4	24	30	30
Verbal fluency (total)	105	37.3	12.1	15	78	-
Moray House Test	99	57.6	8.4	30	74	76
RSPM	102	30.9	8.1	12	51	60
Logical Memory Total	104	33.0	11.6	6	74	100

MMSE = Mini-mental state examination
NART = National Adult Reading Test
RSPM = Raven's Standard Progressive Matrices

WML and cognitive function. As described in Chapter 4.2.3, (correlations between WML and cognitive test score (Table 4.7) were all in the expected direction, with only the association between MMSE and PVH reaching conventional statistical significance (ρ = -.21, P = .02).

DTI and cognitive function. Correlations between DTI parameters and cognitive tests are shown in Table 5.4. Generally, as hypothesised, <D> was negatively correlated with cognitive test results, and FA positively correlated. In the three general

correlations for general ability (MMSE), prior ability (NART) and fluid ability (*g*) conventional statistical significance ($P < .05$) was reached only for MMSE in centrum semiovale for <D> ($\rho = -.15$, $P = .04$). When the relationship between DTI and verbal fluency alone was considered, there was a relationship between <D> and verbal fluency in all brain areas between (r from -.22 to -.27; P from .028 to .009), and between FA and verbal fluency in the occipital region ($r = .25$, $P = .01$).

To assess the role of potential confounders, namely WML load, whole brain volume, age, sex and prior ability (estimated by NART), partial correlation was performed on the cognitive tests and DTI parameters controlling for these variables. All associations were attenuated, but the associations with verbal fluency remained (<D> frontal white matter: $r = -0.21$, $P = 0.05$; <D> occipital white matter: $r = -0.23$, $P = 0.03$; <D> centrum semiovale: $r = -0.14$, $P = 0.19$; FA occipital white matter: $r = 0.19$, $P = 0.08$). None of the other cognitive tests, including the *g* factor, had a significant association with DTI parameters when corrected for these potential confounders.

Analyses were repeated excluding 10 subjects with prior infarction on MRI. All associations were attenuated, but the association with verbal fluency remained statistically significant (<D> frontal white matter: $r = -0.21$, $P = 0.04$; <D> occipital white matter: $r = -0.22$, $P = 0.04$; <D> centrum semiovale: $r = -0.19$, $P = 0.06$; FA occipital white matter: $r = 0.23$, $P = 0.03$). There were no significant correlations between whole brain volume and DTI parameters (r ranging from -0.03 to 0.16, P all > 0.1).

Table 5.4: Correlations between DTI parameters and cognitive ability (Pearson's r except MMSE = Spearman's ρ)

	<D>						FA					
	Frontal		Occipital		Centrum		Frontal		Occipital		Centrum	
	r	P	r	P	r	P	r	P	r	P	r	P
Hypothesis	Neg		Neg		Neg		Pos		Pos		Pos	
NART	-.07	.51	-.08	.41	-.10	.31	.04	.68	.11	.26	.09	.34
MMSE	-.18	.073	-.15	.13	**-.21**	**.038**	.07	.51	.02	.84	-.02	.88
g	-.08	.44	-.18	.08	-.15	.14	-.00	.97	.13	.20	.14	.15
VF	**-.25**	**.009**	**-.27**	**.006**	**-.22**	**.028**	-.07	.49	**.25**	**.01**	.07	.46
RSPM	-.06	.58	-.09	.37	-.10	.30	-.02	.83	.02	.86	.08	.39
MHT	-.09	.40	**-.21**	**.043**	-.14	.16	.13	.20	.17	.09	.11	.28
LM	.02	.82	-.06	.56	-.12	.23	-.02	.82	-.08	.44	.12	.23

Bold type: P <.05

Neg = Negative

Pos = Positive

NART = National Adult Reading Test
MMSE = Mini-mental state examination
RSPM = Raven's Standard Progressive Matrices
LM = logical memory

VF = verbal fluency
g = general cognitive factor
MHT = Moray House Test

Vascular risk factors. Since WML are thought to have a vascular aetiology, the influence of vascular risk factors on DTI parameters was investigated. The DTI parameters were compared between those with or without vascular risk factors or a diagnosis of vascular disease using ANOVA. There were no significant differences in cognitive test scores for those with or without a history of diabetes, hypertension, and cardiovascular or cerebrovascular disease. For DTI parameters those with a history of hypertension had higher <D> frontally ($F_{(1,102)} = 4.81$, P = 0.03) and those with a history of cerebrovascular disease had higher <D> in all areas (frontal white matter: $F_{(1,102)} = 8.9$, P <0.01; occipital white matter: $F_{(1,102)} = 12.0$, P <0.01; centrum semiovale: $F_{(1,100)} = 4.1$, P <0.05) and lower FA in frontal and occipital regions (frontal white matter: $F_{(1,102)} = 5.1$, P = 0.03; occipital white matter: $F_{(1,102)} = 7.7$, P <0.01). There were no differences in DTI parameters for those with or without an infarct on MRI. There were no statistically significant associations between DTI parameters and measured blood pressure (BP) or body mass index (BMI), and no significant differences between current, ex and non-smokers.

If analyses were restricted to only those with no history of cerebrovascular disease (n = 95) all associations were attenuated. A statistically significant association remained for WML: between MMSE and PVH ($\rho = -.20$, P = .049); the association between MHT and PVH became significant ($\rho = -.21$, P = .045) (Table 5.5).

Table 5.5: Correlations between WML and cognitive ability (Spearman's ρ) restricted to those without history of cerebrovascular disease (n = 95)

	PVH		DWMH	
	r	P	r	P
NART	-.03	.75	-.00	.98
MMSE	**-.20**	**.05**	-.05	.60
g	-.14	.17	-.07	.48
VF	-.10	.35	-.01	.88
RSPM	-.19	.07	-.12	.24
MHT	**-.21**	**.04**	-.04	.67
LM	-.00	.96	-.02	.83

Bold type: P <.05

None of the correlations between DTI and cognitive function reached statistical significance when restricted to 95 without a history of cerebrovascular disease (Table 5.6).

Table 5.6: Correlations between DTI parameters and cognitive ability (Pearson's r except MMSE = Spearman's ρ) restricted to those without history of cerebrovascular disease (n = 95)

	<D>						FA					
	Frontal		Occipital		Centrum		Frontal		Occipital		Centrum	
	r	P	r	P	r	P	r	P	r	P	r	P
NART	-.04	.70	-.06	.55	-.08	.41	-.00	.98	.10	.32	.14	.17
MMSE	-.08	.44	-.07	.50	-.16	.13	.03	.80	.00	.99	.01	.94
g	.01	.96	-.12	.27	-.13	.22	-.04	.71	.09	.43	.19	.08
VF	-.17	.10	-.18	.08	-.18	.09	-.10	.33	.19	.06	.12	.23
RSPM	-.01	.93	-.05	.61	-.09	.40	-.04	.70	-.02	.85	.09	.38
MHT	-.05	.66	-.19	.08	-.15	.15	.12	.26	.14	.17	.15	.15
LM	.09	.39	-.03	.80	-.10	.33	-.07	.50	-.15	.16	.08	.41

Bold type: P <.05

5.4 Discussion

In this chapter differences between the DTI parameters of different brain regions have been shown, with the frontal area having the lowest <D> and highest FA. Even within this narrow age range (75 to 81 years), there was an association between age and <D>, but not FA. DTI parameters correlated more strongly than WML load with cognitive ability. There was a trend towards an association between worse cognitive function and increased <D> and decreased FA, with the results were most consistent for verbal fluency and diffusivity. Those with a history of cerebrovascular disease had higher <D> and lower FA, and there was a correlation between <D> and WML. The association between <D> and VF persisted when corrected for WML.

This is the largest study to date in which relationships among WML load, water diffusion parameters and cognitive function have been investigated in older people. A major strength of this study is the inclusion of a cohort of community-dwelling older subjects with a narrow age range, namely 75-81 years, which is significantly older than most published studies. Since the main correlate with cognitive function is normally age, studying a cohort with a narrow age range allows the relationship

between brain MRI data and individual differences in cognitive ability to be investigated (Hofer, Berg, & Era, 2003).

These data therefore add to the current literature in three main areas. Firstly, the use of a sample from the community, whose only exclusion criteria were severe physical or mental illness, means that the values for <D> and FA can be used as reference values for typical older people. For example, <D> is generally higher, particularly frontally, than previously published cohorts, which used people referred for clinical investigations (Head et al., 2004), hospital workers (Abe et al., 2002), and/ or younger (Chen et al., 2001; Chun et al., 2000; Helenius et al., 2002) subjects. This is consistent with changes described with increasing age. The FA values are very similar to those published in healthy middle age (Sullivan et al., 2003; Helenius et al., 2002) except for reduced FA in frontal regions. This may be due to ageing changes disproportionately affecting the frontal lobes (Hedden et al., 2004; Bartzokis et al., 2003; Abe et al., 2002). The fact that there were significant differences between brain regions, with frontal white matter having the highest <D> and lowest FA, also shows the importance of ROI selection. Cross-sectional studies that compare old with young groups should consider differences within, as well as between, these groups. The fact that, even within a six-year age band, <D> changes with increasing age is important when comparing cohorts of people. This would urge caution in studies which use groups of people of similar age as a homogeneous group: differences within such groups can be as large as between them (Helenius et al., 2002). Initially there appeared to be a sex difference in brain <D>, but this was confounded by the small number of men in the cohort being older than the women, and once age was accounted for, there was no longer a sex difference. The majority of studies which have investigated a sex difference in DTI parameters have found none (Pfefferbaum et al., 2003; Abe et al., 2002; O'Sullivan et al., 2001a; Virta et al., 1999). The association between age and <D> was seen for all brain regions, whereas there were no significant associations with FA, and indeed the association in the frontal area was in the opposite direction than expected. This may be due to the exact placement of ROI, particularly important for FA.

Secondly, the cognitive correlates of both WML and DTI parameters were considered in the same study. Some studies relating DTI data to cognitive ability have not accounted for WML in their analyses (Madden et al., 2004; Stebbins et al., 2001b). Increased <D> and decreased FA have been shown both within WML, and in surrounding normal-appearing white matter (O'Sullivan et al., 2001b; Jones et al., 1999). Thus, changes detected by DTI are not restricted to areas that are abnormal on T_2-weighted MRI, and it is important to consider WML burden in DTI studies of older people. Previous studies have found statistically significant associations between (1) <D> and cognition: anterior white matter <D> with executive function (O'Sullivan et al., 2001a), and centrum semiovale <D> with MMSE (Shenkin et al., 2003); and (2) FA and cognition: frontal white matter FA with executive function (Shenkin et al., 2003) and verbal reasoning (Shenkin et al., 2003); middle white matter FA with verbal fluency (O'Sullivan et al., 2001a); and centrum semiovale FA with prior IQ and verbal reasoning (Shenkin et al., 2003) (Chapter 1.1.3.2; Table 1.3). The current study is the largest study of DTI and cognition to date (previous largest n = 31), and although there was a trend in the expected direction, the only statistically significant association between white matter water diffusion parameters and three broad measures of cognitive ability (NART, MMSE and *g*) was for centrum semiovale <D> and MMSE. Thus, as the sample sizes have increased, the effect size of the correlation has decreased (from a correlation coefficient of 0.4 to 0.9, to 0.1 to 0.2 in this study), implying that the true effect is nearer to that found here. However, the most consistent and strongest association between cognitive tests and DTI parameters was between verbal fluency, a non-specific measure of executive function, and <D>. Interestingly, this negative correlation was present in all regions studied, not just the frontal region. This agrees with a previous small DTI study (O'Sullivan et al., 2001a) and neuroimaging evidence that suggests that executive functions are more widely distributed throughout the brain than previously thought (Carpenter, Just, & Reichle, 2000) or that skills involved in verbal fluency are varied, including, for example, retrieval. These findings indicate that executive function may be the cognitive domain most sensitive to subtle, diffuse, age-related deterioration in white matter integrity. If verbal fluency was merely selected from the correlation matrix for focus, this approach could be criticised, but it was a hypothesis

we intended to test *a priori*. Furthermore, the possibility of these results being prone to Type I error is reduced by the large number of subjects, indicating tight confidence intervals around the coefficient, combined with the fact that the significant correlations are not randomly spread throughout the matrix. A Bonferroni correction for multiple testing is not appropriate here, as the variables are intercorrelated (Perneger, 1998). We did not replicate the result from our previous study, which showed an association between FA, and not <D>, and prior ability. The earlier result from the smaller study may have been a type I error, but it is possible that the initial subgroup were different from the overall cohort, perhaps because they were the oldest of the group (all aged 80-81). It is still important that studies of cognitive ageing consider the participants' prior ability (Deary et al., 2004b).

Finally, since WML are thought to have a vascular aetiology (Schmidt et al., 2004) the influence of vascular risk factors on DTI parameters was also considered. Those subjects with higher WML load had higher <D> in normal-appearing white matter than those with fewer WML, which is consistent with previous studies (O'Sullivan et al., 2001b; Jones et al., 1999). This suggests that DTI changes might detect pathologic white matter damage at an early stage, thereby allowing interventions to prevent progression to WML. Potential targets for such interventions include vascular risk factors. Significant differences were found in DTI parameters between those with and without a history of vascular disease or hypertension. Those with hypertension had higher <D>, consistent with the literature showing hypertension as the vascular risk factor with the most robust association with WML (Longstreth, Jr. et al., 1996). Those with a history of cerebrovascular disease, also known to be associated with WML (Longstreth, Jr. et al., 1996; Vermeer et al., 2003a) had higher <D> and lower FA. Significant negative correlations were also observed between <D> and FA for all three brain regions studied in this cohort. Such correlations have been reported previously by Pfefferbaum and Sullivan (2003) in the genu, splenium and centrum semiovale of 64 normal volunteers aged 23-85 years, and by Head et al. (2004) in frontal, temporal, parietal and occipital white matter regions in 25 young adults aged 19-28 years, 25 non-demented older adults aged 69-88 years and 25 age-matched older adults with Alzheimer type dementia. In both studies, the correlations

were strongest for the older subjects, especially the Alzheimer dementia group. These data suggest that increasingly significant correlations between <D> and FA are indicative of pathological change in white matter, with cerebrovascular disease being one possible mechanism in normal ageing (Head et al., 2004). Countering the argument that <D> and FA can be used as measures relating to cerebrovascular disease is the finding that measured BP (arguably more sensitive than self-reported history), was not related to DTI. However, BP may have been affected by treatment or attendance at the clinic. DTI parameters are known to change in the evolution of stroke (Munoz et al., 2004) and cerebrovascular disease is associated with cognitive impairment (O'Sullivan et al., 2004). Therefore using DTI to investigate relationships between vascular risk factors, cerebrovascular disease, cognition and white matter integrity is a promising area for future research.

The current study has several potential weaknesses. The first of these is the use of a volunteer community-dwelling sample, which raises the possibility of selection bias. In general, study volunteers tend to be of higher socio-economic status and better educated than non-participants (Deary et al., 2004b; de Groot et al., 2000). This may lead to a restricted range of results, and thus a conservative estimate of any association. It is also possible that subjects with underlying illness were more (or less) likely to volunteer, due to the potential for medical assessment, although we found a prevalence of vascular risk factors similar to studies where subject selection attempted to be representative of the population (e.g. Longstreth, Jr. et al., 1996). These potential biases should be considered when extending these results to other samples and populations. Underlying pathology may affect the relationship between cognitive ability and brain ultrastructure changes. We considered this in the context of vascular risk factors, and although there were no differences in cognitive ability parameters for those with or without a history of vascular risk factors, those with a history of cerebrovascular disease had higher <D> and lower FA. The exclusion of these subjects from the analyses meant the relationship between DTI parameters and verbal fluency was no longer statistically significant. However, correcting for confounders including WML in the correlation did not eliminate the relationship. These results suggest that there is not a simple progression from DTI changes to

WML to cerebrovascular disease. The relationship between DTI, WML and both clinical and radiological evidence of cerebrovascular disease requires further investigation, such as cross-sectional and longitudinal studies comparing different imaging modalities and clinical presentations of CVD.

The second potential weakness of this DTI study is the use of ROI methodology. Although we employed an ROI method previously used in studies of ageing and cognition (Shenkin et al., 2003; O'Sullivan et al., 2004; O'Sullivan et al., 2001b) the subjective nature of ROI placement remains a problem in the study of normal subjects. ROI analysis is well-suited to the study of focal disease, but is more difficult in normal subjects. This particularly affects FA, and is because FA is exquisitely sensitive to the position of an ROI, and adjacent ROI can have very different FAs depending on where they are placed relative to white matter tracts (Nusbaum et al., 2001). This issue principally affects the measurement of FA, since even small variations in ROI location will produce significantly different results depending on where the ROI is placed relative to the white matter tracts (Pfefferbaum et al., 2003). <D> is less sensitive to these effects, which may explain why our results were more consistent for <D> than FA. This problem could be addressed by defining the ROI co-ordinates in Talairach space and determining the corresponding location in the subject's native space (Salat et al., 2005) Talairach space is defined in a stereotactic atlas based on the brain of a 60 year old right-handed French woman, and has been widely used as a reference template in functional imaging. This allows structural and functional data to be transformed to a common coordinate reference system (Weiss et al., 2003). Therefore, a ROI defined in Talairach space can be manipulated mathematically to define a ROI on the subject's native space. It may, however, be difficult to register elderly brains accurately to a standard template. Alternatively, segmenting the brain's entire white matter volume would allow histogram measurements of <D> and FA to be obtained from large areas of white matter without subjective placement of ROI (Chun et al., 2000), but this also has problems because of the inclusion of different structures (e.g. white and grey matter) (Pfefferbaum et al., 2003). However, the presence of white matter lesions makes both approaches far more problematic than in younger people. We avoided placing ROI on

obvious white matter lesions, but previous studies have shown that in subjects with relatively high WML load, even normal appearing white matter will have relatively high <D> (Firbank et al., 2003) and low FA (O'Sullivan et al., 2001b). Further work is required to determine what the optimum method is for measuring water diffusion parameters reproducibly in the brains of older people with atrophy and white matter disease.

Studies of DTI are difficult to compare due to the different methodologies used in different centres, which ranges from the basic set-up of the imaging parameters, through the selection of regions of interest, to the methodology used to generated the <D> and FA values (Sullivan et al., 2003). There is no established gold standard for DTI (Moseley et al., 2002), or indeed for a cognitive test battery sensitive to ageing. Future studies of cognitive ageing should include standard brain areas e.g. corpus callosum, cerebral peduncle, centrum semiovale, and standard cognitive tests e.g. MMSE, NART, verbal fluency and other tests of executive function, to allow comparison between studies.
Advances in technology allow the combination of imaging techniques in protocols that are short enough to be tolerated by older people. There is a need for cross-sectional, and ultimately, longitudinal studies that compare the results from different methodologies (e.g. DTI, fMRI). For example, Madden et al (Madden et al., 2004) used fMRI and DTI to compare the response time of older with younger people. Response time correlates with IQ score (Der & Deary, 2003). They found that in the younger group FA of the anterior limb of the splenium accounted for 29% of the variance in RT, whereas for the older group, FA of the internal capsule accounted for 30% of their variance in RT. This, when combined with the fMRI results suggested that older people's performance depended on both cortical activation and white matter integrity within corticostriatal circuits, whereas for younger people performance depended mostly on the white matter integrity of posterior regions mediating visual processing.

DTI has been hailed variously as the "'Holy Grail' of diagnostic imaging or …a game of numbers" (Herneth, 2003) (p.167). It certainly has great promise and is

being used increasingly in both clinical and research settings. However, there is no established gold standard to assess the measurement limits and errors (Moseley et al., 2002). Studies of DTI are difficult to compare due to the different methodologies used in different centres. This ranges from the basic set-up of the imaging parameters, through the selection of ROIs, to the methodology used to generated the <D> and FA values. The intuitive appeal of this imaging technique may have led to researchers "jumping to conclusions not supported by the data" (Keir & Wardlaw, 2000) p. 2728.

There are many methodological issues to be resolved with DTI, but it is a useful tool to investigate structure-function relationships in vivo. In addition, there is the possibility of using DTI to screen people at risk of cognitive decline, or to assess the influence of treatment (O'Sullivan et al., 2004). Our study cautions against some strong claims made by smaller studies, and proposals that DTI could be used as an alternative to cognitive tests (Moseley et al., 2002). It does, however, suggest that DTI can add to our understanding of the anatomy of cognitive impairment in normal older people, and that executive function may be the cognitive domain most sensitive to cerebral disconnection.

In this chapter, relationships between cognitive ability and both WML load and DTI parameters in a large group of community-dwelling older people aged between 75 and 81 years were investigated. There was a trend towards increased WML load correlating with poorer cognitive function, and this trend was statistically significant for the MMSE. Correlations were found between DTI parameters and cognitive ability, specifically verbal fluency and <D>. This indicates that executive function may be the cognitive domain most sensitive to age-related decline in white matter tract integrity. DTI therefore may be a useful tool to investigate the anatomy of early cognitive impairment in normal older people.

6 Contribution of early life factors to cognitive ability

In this chapter the contribution of various early life factors to cognitive ability around age 80 is considered. Firstly the relationship between cognitive ability and measurements around birth, particularly birth weight, but also birth length and placental weight, is examined (Chapter 6.1). Secondly the importance of social class at birth is considered (Chapter 6.2). These parameters are considered alone and in conjunction with potential confounders (e.g. maternal age, parity). Finally, the relationship between the *APOE* gene and cognitive ability is assessed in this cohort (Chapter 6.3).

6.1 Birth parameters and cognitive ability

6.1.1 Introduction

Several studies have confirmed a small, but significant, relationship between birth weight in the normal range and cognitive ability in childhood, independent of social class (reviewed in Shenkin et al., 2004 and Chapter 1.2). Few studies have investigated the relationship between birth weight and cognitive ability in older age (reviewed in Chapter 1.2, summary in Table 1.1 and 1.2 and Figure 1.1). Two studies at army recruitment (age about 17) found a non-linear relationship between birth weight and cognitive ability (Seidman et al., 1992; Sorensen et al., 1997). One study followed children longitudinally into middle age, and found an association between birth weight and cognitive ability age 43, but this was mainly accounted for by persistence of the relationship from age 8 (Richards et al., 2002). Two studies of older people (age 60-70) found no significant relationship between birth weight or length and cognition, although there was a trend in the expected direction (Martyn et al., 1996; Gale et al., 2003).

These studies were not restricted to normal birth weights, although some reported results excluding births <2,500g, and found the relationship between birth weight and cognitive ability persisted (e.g. Richards et al., 2002). Not all of these studies were able to account for gestational age (e.g. Richards et al., 2002), and where possible birth weight should be corrected for gestational age as weight increases with gestation. None of these studies had details of placental size. The placenta is the

mechanism whereby oxygen and nutrients are transported to the fetus, and therefore its integrity should be a consideration when examining prenatal influences on growth and development (Sibley et al., 2002; Jackson, 1996; Gagnon, 2003). Placental integrity can be crudely measured by placental weight, although the use of this has been criticised because of the importance of factors other than weight, and the substantial measurement error in assessing placental weight. However, placental weight, and placental weight relative to birth weight, has been found to predict essential hypertension in adulthood (Barker, Bull, Osmond, & Simmonds, 1990) and should therefore be considered when assessing prenatal influences on later life outcomes. If placental weight reflects placental integrity, and placental integrity is required for adequate nutrition and oxygenation of the fetus, placental weight might be expected to relate to increased cognitive ability.

Birth length and birth weight are highly correlated, and therefore birth length might also be expected to correlate with cognitive ability. Previous studies have considered the relationship between birth weight and length using ratios such as the ponderal index (weight/length^3) but this has been shown to be less reliable and valid as a predictor of intrauterine growth retardation than birth weight alone (Haggarty, Campbell, Bendomir, Gray, & Abramovich, 2004), and is not considered here.

In the Simpson's study the relationship between birth weight, length, and placental size with cognitive ability in old age was investigated. The hypotheses were firstly, that there would be a small but statistically significant positive association between birth weight and cognitive ability around age 80. This would be attenuated when corrected for confounders. People who score well on cognitive tests later in life generally perform well earlier in life (Deary et al., 2000). Therefore, the second hypothesis was that the correlation between birth weight and cognitive ability in older age would substantially be accounted for by a persistence of this relationship from earlier life, i.e. the association would also be attenuated when corrected for childhood ability. The final hypothesis was that there would be a positive association between birth length and cognitive ability, and placental weight and cognitive ability.

6.1.2 Methods

The methods for recruitment, neuropsychological testing and archive data retrieval are described in Chapter 2.

6.1.3 Statistical analyses

Mean cognitive test scores for 500g categories of birth weight are presented. The associations between cognitive ability in old age and measures of fetal development (birth weight, birth length, placental weight) were described using Pearson's r (apart from MMSE which showed a ceiling effect, and was therefore analysed using Spearman's ρ). Simple linear regression was used to investigate the association between birth weight and cognitive tests, and multiple regression to assess the influence of potential confounders in early life (sex, gestational age, parity, maternal age, paternal social class).

6.1.4 Results

Descriptive statistics for cognitive test results and measures of fetal development are shown in Chapter 3 (Tables 3.3 and 3.2 respectively). All cognitive tests were positively intercorrelated (Table 3.4), and principal components analysis was therefore used to derive a general cognitive factor (*g*) from the tests of more fluid ability (Verbal fluency, Raven's SPM, Moray House Test, Logical Memory). The first unrotated principal component accounted for 50.7% of the total variance. Each subject was given a score on this general cognitive factor (*g*), in addition to NART and MMSE scores.

6.1.4.1 Birth parameters and cognitive ability in older age

For simplicity of presentation, and comparison with other studies, cognitive test scores are presented as related to birth weight after it was divided into 500g categories (Table 6.1). NART is presented as an estimate of prior ability (further discussion in Chapter 6.1.4.2), *g* for current fluid ability, with Raven's to allow comparison with absolute values from other studies.

Table 6.1 Cognitive test scores by birth weight divided into categories (n = 110)

	NART			*g*			RSPM		
Birth weight	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**
<2500g	3	22.7	6.5	3	-.67	1.0	3	24.7	9.1
2501-3000g	23	29.3	7.6	21	-.21	1.1	23	28.6	7.4
3001-3500g	43	30.8	8.2	41	.09	.9	41	31.3	7.7
3501-4000g	34	29.1	7.3	31	.00	1.1	33	31.4	9.6
>4000g	7	34.1	9.5	6	.45	.5	7	34.9	2.5

NART = National Adult Reading Test
g = first unrotated principal component from RSPM, MHT, VF and LM (n = 102)
RSPM = Raven's Standard Progressive Matrices

There is a suggestion of an increase in cognitive test score as birth weight increases. To test whether this reaches statistical significance birth weight (as a continuous variable) was correlated with cognitive ability in older age (Table 6.2). Birth weight is presented both raw, and corrected for gestational age (linear regression, birth weight as dependent variable, gestational age as independent variable, saving standardised residuals). Birth length and placental weight, and their relationship with cognitive ability, are also presented. There is a consistent positive correlation between birth weight and cognitive ability (r = .07 to .23) although this did not always reach conventional statistical significance. Correcting for gestational age slightly strengthened the correlation with most cognitive variables (r = .09 to .25). The strongest associations are between birth weight and MMSE (ρ = .23), Raven's Matrices (r = .20) and *g* (r = .16).

The associations between birth length and cognitive ability are generally positive, but none reach statistical significance (r ~ .1, range -.09 to .15). There is a similar pattern for placental weight (r ~.1, range -.02 to .16). Relationships between cognitive ability and birth length or placental weight are not further considered here.

Table 6.2: Correlation between cognitive ability in older age and birth measurements

	MMSE		*g*		RSPM		MHT		VF		LM		NART	
	ρ	P	r	P	r	P	r	P	r	P	r	P	r	P
BW (n=110)	**.23**	**.02**	.16	.11	**.20**	**.04**	.12	.21	.07	.47	.07	.45	.11	.26
BW c GA (n=100)	**.21**	**.04**	**.23**	**.03**	**.25**	**.01**	.16	.12	.13	.18	.09	.38	.14	.17
BL (n=107)	-.09	.33	.15	.12	.11	.26	.09	.35	.09	.35	.03	.79	.10	.32
PW (n = 83)	.16	.14	.07	.53	.11	.30	.08	.47	-.02	.87	.07	.52	.02	.83

Bold type: P <.05

BW = Birth weight
BW c GA = Birth weight corrected for gestational age
BL = Birth length
PW = Placental weight

MMSE = Mini-Mental State Examination (n = 107)
g = first unrotated principal component from RSPM, MHT, VF and LM (n = 102)
MHT = Moray House Test (n = 104)
VF = Verbal Fluency
LM = Logical Memory (n = 109)
NART = National Adult Reading Test

Scattergrams of birth weight and each cognitive test were examined to exclude non-linear relationships, which would be an alternative explanation for non-significant correlations (Appendix 9.10). These did not show any consistent pattern: there is a suggestion of a decrease in cognitive ability scores at birth weight of <3,000g (rather than the conventional definition of low birth weight of <2,500g) but there were no statistically significant difference in cognitive ability between those born below or above 3,000g (t-test (equal variance assumed) MMSE t = -2.0, P = .05; NART t = -1.1, P .29; RSPM t = -1.9, P .06; MHT t = -1.2, P = .24; VF t = -.88, P = .38; LM t = -1.2, P = .24). In addition, non-parametric correlations were performed for birth weight and each test, giving similar results (ρ = .07 to .23) (Appendix 9.11).

If the small numbers of births outwith the normal range (n = 3 < 2,500g; n = 1 > 4,500g) are excluded the correlations are similar (birth weight and MMSE ρ = -.21; P = .03; *g* r = .13, P = .2; RSPM r = .16, P = .11; MHT r = .11, P = .26; VF r = .05, P = .62; LM r = .06, P = .54) (Appendix 9.11).

The relationship between birth weight and non-verbal reasoning in old age was examined in more detail using linear regression. Firstly, g was used as the dependent variable, as a composite measure of all fluid-type tests, and secondly Raven's SPM was used as a dependent variable for illustrative purposes, and to allow comparability

with other studies which present data from only one cognitive test (Seidman et al., 1992; Sorensen et al., 1997; Martyn et al., 1996).

The results of a simple linear regression of *g* on the entire birth weight range, not accounting for possible confounders, are shown in Table 6.3.

Table 6.3: Regression analysis of *g* on birth weight (n= 102)

	R	*b*	SE	t	P	95% CI for *b*		Adj R^2
						Lower	Upper	
Constant		-1.2	0.7	-1.6	0.11	-2.6	.25	
BW	0.16	0.0004	0.0002	1.6	0.10	-0.00007	0.0008	0.017

Residual SD = 1.0

As expected from the correlation between birth weight and *g* of .16 (P = .11), the model was not significant.

To check that no extreme outliers had been included, and to check for possible violations of the assumption on linearity, the following additional descriptives were performed. The standardised residuals histogram was adequately symmetrical, and normal P-P plot did not show extreme deviations. Case-wise diagnostics did not identify any outliers with an absolute standardised residual of more than 3. The plot of standardised residuals against standardised predicted values showed no obvious pattern.

The correlation between potential confounders (gestational age, social class (here entered as an ordinal variable, but for further discussion see Chapter 6.2), parity and maternal age) and both *g* and Raven's matrices are shown in Table 6.4. None of these potential confounders correlate significantly with *g*, or Raven's matrices, and if they are added to the model predicting *g* using standard multiple regression, as would be expected, no variables enter the model to predict *g*.

Table 6.4: Bivariate associations between potential confounders and *g* and RSPM

	g		RSPM	
	r	P	r	P
Gest age	.08	.47	-.09	.38
Social class	-.09	.36	-.12	.24
Parity	-.06	.56	-.09	.34
Maternal age	.08	.46	.02	.82

The results of a simple linear regression of RSPM score on the entire birth weight range, not accounting for possible confounders, are shown in Table 6.5.

Table 6.5: Regression analysis of RSPM on birth weight (n= 107)

	R	*b*	SE	t	P	95% CI for *b*		Adj R^2
						Lower	Upper	
Constant		19.2	5.7	3.4	0.002	7.9	30.6	
BW	0.20	0.003	0.002	2.0	0.044	0.0001	0.0068	0.029

Residual SD = 8.0

With RSPM as the dependent variable, birth weight did contribute to the model, with RSPM increasing .3 points (95% confidence intervals .01 to .7) for every 100g increase in birth weight.

For RSPM, descriptive diagnostics were satisfactory: the standardised residuals histogram was adequately symmetrical, and normal P-P plot did not show extreme deviations. Case-wise diagnostics did not identify any outliers with an absolute standardised residual of more than 3. The plot of standardised residuals against standardised predicted values showed no obvious pattern.

None of the potential confounders identified in previous studies correlated significantly with RSPM score (Table 6.4), and none contributed to a multiple regression analysis model of RSPM including birth weight as an independent variable. When potential confounders are included in the model birth weight remains a significant predictor of RSPM score (b = .004, P = .03) (Table 6.6). The overall model does not reach conventional statistical significance (P = .08), and none of the other variables contributes significantly. Therefore the simple linear regression gives

a more accurate estimate of the effect size of the influence of birth weight on RSPM score. 0 to .8 points) (compared to .3 points when confounders not considered).

Table 6.6: Standard multiple regression analysis of Raven's matrices score on birth weight, maternal age, birth order, social class & legitimacy, sex, gestational age, and age at testing (n=97)

	b	SE	beta	t	P	95% CI for *b*	
						Lower	Upper
Constant	83.77	49.88		1.68	0.097	-15.35	182.90
Birth weight	0.004	0.002	0.228	2.21	0.030	0.000	0.008
Maternal age	0.72	0.16	0.06	0.46	0.647	-0.24	0.39
Birth order	-0.61	0.54	-0.14	-1.14	0.259	-1.67	0.455
Social class	-0.74	0.66	-0.12	-1.11	0.268	-2.05	0.58
Sex (female)	-2.80	1.85	-0.15	-1.51	0.135	-6.47	0.88
Gest age	-0.56	0.33	-0.17	-1.67	0.099	-1.22	0.11
Age (years)	-0.51	0.60	-0.09	-0.85	0.399	-1.72	0.69

R	R^2	Adj R^2	SEE	F	df regression	df residual	P
0.36	.128	0.060	8.0	1.87	7	89	.08

Residual SD = 7.7

The coding of variables such as social class can have an effect on the significance of multiple regression models (discussed in Shenkin, 2002). Social class was entered in the model shown in Table 6.6 as an ordinal variable, but this may not be appropriate, as the distances between various social classes are not equal. A more appropriate method may be to code each social class as a dummy (categorical) variable against a reference category (Tabachnick, 2000) (also see Chapter 6.2). Also there is some concern about the accuracy of recall of the last menstrual period and therefore calculation of gestational age. Gestational age was also recoded, therefore, into preterm (<37 weeks) or post-term (>42 weeks), each entered as dummy variables compared to term births, but neither preterm nor post term births contributed to a model of Raven's matrices or *g*.

In summary, there was a small, positive association between birth weight (corrected for gestational age) and mental ability in old age (r ranging from .07 to .23 depending on the cognitive test). For 100g increase in birth weight, Raven's matrices score increased by 0.3 points, birth weight accounting for 2.9% of the variance in Raven's score. If potential confounders were included in the model none contributed

significantly. There was no statistically significant contribution of birth weight to a model with *g* as the dependent variable.

The hypotheses of a positive association between cognitive ability and birth length, and cognitive ability and placental weight, were rejected. Although the associations between birth length and cognitive ability were generally positive, none reached statistical significance (r ~ .1, range -.09 to .15). There was a similar pattern for placental weight (r ~.1, range -.02 to .16).

6.1.4.2 Birth parameters and cognitive ability in childhood

Many studies of older people do not have actual measures of childhood cognitive ability, and therefore estimates of prior ability e.g. NART (Deary et al., 2004b), Mill Hill Vocabulary Test (Martyn et al., 1996), are used. In the Simpson's study we were able to compare results on the NART, tested at age around 80, with actual measures of childhood mental ability where they were available (i.e. for those participants who were born in 1921 and participated in the Scottish Mental Survey 1932: n = 31) (Table 6.7). The correlation between NART and birth weight for the whole Simpson's study cohort (n = 110) was r = .11, but this does not reach conventional statistical significance (P = .26). The strength of the relationship increases when birth weight is corrected for gestational age (r = .14, P = .17). In the subgroup of the Simpson's study (n=31) where results from the MHT age 11 were available, correlation between MHT age 11 and birth weight was again around .1. For these 31 people, the correlation between MHT score and NART was .73, P <.001. This concurs with the validation of the NART in a separate larger sample from Aberdeen (ABC 1921) (Deary et al., 2000).

The correlation between birth weight and results on the MHT age 11 for those who participated in the Simpson's (current) study and who were born in 1921 (n = 31, ρ = .11) can also be compared with the correlation between MHT score and birth weight for the entire group born in 1921 who sat the MHT age 11 and whose birth weight was traced in the Royal Maternity and Simpson Memorial Hospital, but who were not tested in later life (n = 490, see Shenkin et al., 2001; Shenkin, 2002). The correlation coefficient between birth weight and MHT score for the whole cohort of those born in 1921 was around .15, but due to the larger numbers this does reach

conventional statistical significance (P = .001) for birth weight (but not birth length or placental weight).

In the Simpson's (current) study there were no significant correlations between birth length and NART tested at age 75 to 81 (r = .10, P = .32) or placental weight and NART (r = .02, P = .83), and these variables are not considered further here.

Table 6.7: Correlation between cognitive ability in childhood (estimated and measured) and birth measurements

	NART (n=110)		MHT age 11 (n=31)		MHT age 11 (n=490)	
	r	P	ρ	P	r	P
Birth weight (n = 110)	.11	.26	.11	.56	**.15**	**.001**
BW corr for GA (n=100)	.14	.17	.11	.60	**.17**	**.001**
Birth length (n = 107)	.10	.32	-.06	.75	.09	.06
Placental weight (n = 83)	.02	.83	-.22	.64	.14	.12

Bold type: correlation significant at P < .05
BW corr for GA = birth weight corrected for gestational age
NART = National Adult Reading Test MHT = Moray House Test

These results show a consistent correlation between birth weight and early life cognitive ability of around .1; although depending on the sample size this does not reach conventional statistical significance.

The results have been published of those born in the Royal Maternity and Simpson Memorial Hospital in 1921 whose MHT score from 1932 was traced (n = 490) (Shenkin, 2002; Shenkin et al., 2001). With MHT score as the dependent variable and birth weight alone as independent variable, birth weight did contribute significantly to MHT score age 11: adjusted R^2 = .022, *b* = .004 SE = .003, 95% CI .002 to .007; i.e. birth weight accounted for 2.2% of the variance in MHT score, and for 100g increase in birth weight, MHT score increased by 0.4 points. Adding potential confounders, adjusted R^2 = .16, birth weight = *b* .006, SE = .001, 95% CI .003 to .008 (social class, parity, maternal age and child's exact age at sitting the test also contributed significantly to the model); i.e. if potential confounders were taken

into account, this model explained 16% of the variance in MHT score, with 100g increase in birth weight corresponding to 0.6 points increase in MHT score.

Cognitive test scores throughout life are highly correlated, and if this is taken into account by correcting late life scores for early life scores (standardised residuals, old age test score (RSPM or *g*) as dependent variable and NART as independent variable) the association between birth weight and late life ability is attenuated and no longer statistically significant (Table 6.8).

Table 6.8: Correlation between cognitive ability in old age corrected for earlier life, and birth measurements

	g		***g* corr NART**		**RSPM**		**RSPM corr NART**	
	r	**P**	**r**	**P**	**r**	**P**	**r**	**P**
Birth weight (n = 110)	.16	.11	.13	.17	**.20**	**.04**	.15	.12
BW corr GA (n=100)	**.21**	**.04**	.17	.09	**.25**	**.01**	.19	.06

Bold type: correlation significant at P < .05
Corr = corrected for

In summary, there was a small, positive association between birth weight (corrected for gestational age) and mental ability as assessed by RSPM, around age 80, but this was partly accounted for by an association between birth weight and cognitive ability in earlier life (the proportion of variance in RSPM score explained by birth weight decreasing from 6.2% to 3.6% when correcting for an estimate of prior ability, i.e. a decrease in variance explained of 50%).

6.1.5 Discussion

This study found a small positive association between birth weight and cognitive ability around age 80, which was only statistically significant for MMSE and Raven's matrices (not other individual cognitive tests or the general cognitive factor *g* derived from RSPM, Moray House Test, Verbal Fluency and Logical Memory). This relationship was strengthened slightly when correcting for potential confounders including social class, but was attenuated when correcting for earlier life ability, although the association between birth weight and NART did not reach statistical

significance. There was no significant correlation between other birth parameters (birth length, placental weight) and cognitive ability in old age.

This is consistent with a previous study which found a small positive association between birth weight and cognitive ability in later life (Richards et al., 2001). In the British 1946 Birth cohort there was a positive linear association between birth weight category and cognitive score at age 8, 11, 15, 26, and weakly (not statistically significant) at 43 for verbal memory. The effect of birth weight on tests scores at later ages was largely accounted for by its effect earlier in life. Further analyses of this cohort have shown that birth weight is not a marker for postnatal body size, and therefore suggests that prenatal influences are important for cognitive ability (Richards et al., 2002). Two studies of people in older age did not find a statistically significant relationship between birth weight and cognitive ability around age 70, although there was a trend towards a positive association. For example, in Martyn et al. (1996) the correlation between birth weight and AH4 score was positive but non-significant (P = .17). There was no association between birth weight and cognitive decline, which was measured by Martyn et al. by subtracting the standardised test score on the AH4 from that on the Mill Hill vocabulary test. In Gale et al (2003) AH4 test score increased by .63 points (95% CI -1.33 to 2.60) for every kilogram increase in birth weight (P = .52).

Previous studies have suggested that head size may be more important than body size as a predictor of later cognitive ability. For example, Martyn et al (1996) found an association between a measure of head size at birth (biparietal diameter) and cognitive ability (mean age 60.9 years). The association with biparietal diameter may, however, have been due to chance, as multiple correlations were performed, this was not a hypothesis they intended to test, and there were no significant correlations with other measures of head size (head circumference or occipitofrontal diameter). Gale et al. (2003) did not find a significant association between head circumference at birth and later ability (mean age 69.8 years). The Simpson's study did not have any measures of head size at birth.

The lack of statistical significance despite consistent small positive associations suggests that this study lacked power to reliably form conclusions about small associations around .1. With a sample size of 115 we have 90% power to detect a statistically significant association of .27. Thus we found a statistically significant association between birth weight and RSPM (and MMSE), but not other cognitive tests. Notably the association with estimated prior ability (NART) did not reach conventional statistical significance, but correcting RSPM for NART did attenuate the relationship. This suggests that the association between birth weight and cognitive ability around age 80 may be explained in part by the association in early life, but there may still be a persistent influence of birth weight on later ability, even after potential confounders are considered. This study did not have adequate power to further investigate this. To demonstrate statistical significance ($P < .05$) with 90% power with a correlation coefficient of .1 would require a sample size of 850, and with a correlation coefficient of .2, a sample size of 220 (620 and 150 respectively for 80% power) (UCLA department of statistics, 2005). We estimated that our initial target of 150 subjects would give us adequate power for the analyses including examination of cerebrovascular disease. However, the very specific inclusion criteria for this study (place of birth) and data protection concerns limited the recruitment strategies which could be used (see Chapter 2) and we did not reach our initial target. Future studies should be explicit in stating their power calculations prior to recruitment and analyses.

All cohort studies suffer from large proportions of missing data. The individuals who volunteer to take part in studies are generally of higher cognitive ability and social class than those who do not. However, this would bias the results in this study only if the relationship between birth weight and cognitive ability differed between these two groups. Studies that have examined the effect of attrition in longitudinal studies have demonstrated that it does not bias estimates of cognitive change, and has little effect on the strength of associations between variables (Deeg, van Tilburg, Smit, & de Leeuw, 2002). The ability to correct for confounding depends on the data collected, and for example, Richards et al. (2001, 2002) were not able to correct for gestational age. Correction for social class is necessarily crude, and there may be

residual confounding by social factors not included in the methods used for coding for social class (studies which include large numbers of siblings, e.g. Matte et al., 2001, are able to control for the majority of the within-family environment). It was surprising that there was no contribution from potential confounders in this study, as previous studies that have found a positive relationship between birth weight and cognitive ability have also found a (stronger) relationship between social background and cognitive ability (Shenkin et al., 2001; Richards et al., 2002). The relationship between social class and cognitive ability is examined further and discussed in Chapter 6.2.

The use of an estimate of prior cognitive ability is less valid than an actual prior measure, although few studies have access to early life cognitive data. We were able in this study to validate our estimate with actual measures of prior ability in a proportion of our sample. The finding that the association between birth weight and cognitive ability aged about 80 was attenuated by correcting for earlier life ability is consistent with the importance of the life-long trait of intelligence (Deary et al., 2004b). However, although the correlation falls below conventional statistical significance, the effect size does not alter by much (r .25 to .19), and there is therefore still a suggestion birth weight does exert some influence on later life ability not accounted for by prior ability. Other studies have suggested that an important influence is education (Richards & Sacker, 2003), but in this study there was little variance in education received (most subjects leaving school at the start of the Second World War) and this influence could not be investigated here.

All studies collecting data from early life and old age, by definition, will be based on subjects born many decades ago, and thus be susceptible to cohort effects (Ebrahim, 1996). Early life circumstances 80 years ago, in the 1920s, were very different from today, with high perinatal and maternal mortality, different nutritional influences and socioeconomic circumstances (Shenkin, 2002), (Chapter 3). In particular, these individuals were born into a post-war environment, and then were subject to the Second World War as they emerged into adulthood. Any conclusions from the Simpson's cohort may well not be relevant to other populations, but they are

nonetheless valuable. Firstly, comparison of results from different epochs allows similarities and differences to be identified, highlighting influences that may remain stable over time. Secondly, these data provides information about subjects significantly older than previous studies (Martyn et al., 1996; Richards et al., 2002), who will have to wait a decade or more to study individuals in their eighties.

The lack of any association between cognitive ability and birth length or placental weight may reflect a true lack of relationship, or may be the result of other factors. For example, birth length and placental weight are much more susceptible to measurement error than birth weight (Ward, 1993). Birth length was measured to the nearest half inch, and often recorded as whole inches, raising the suggestion of terminal number bias. This decreases the variance in the data and therefore reduces the chance of finding a positive association. Different house surgeons will have performed these measurements, as they changed every three months in the Royal Maternity and Simpson Memorial Hospital, and no data are available for interindividual reliability. Analyses of the four doctors working in 1921 shows that birth length and placental weight were less reliably measured than birth weight (Shenkin, 2002) (Chapter 4.1.3), and recent studies confirm the difficulty in measuring placental weight (Hargitai, Marton, & Cox, 2004). It is interesting that, at birth, weight appears to correlate more strongly than length with later cognitive ability, whereas in later childhood and adulthood height is a stronger predictor than weight of cognitive ability (Tuvemo, Jonsson, & Persson, 1999; Johnson, 1991). This underlines the importance of a life course approach when considering influences on later ability (Kuh et al., 2004a). Both absolute values of weight and height, and changes across the life course should be considered. These may interact (e.g. small babies who 'cross centiles' by increasing weight or height faster than would be expected) (Lucas et al., 1999) or independently influence (Richards et al., 2002) later life outcomes.

Overall, the influence of birth weight on cognitive ability is small, and clearest for RSPM and MMSE, but it is important because it suggests that variations in the prenatal environment have long term effects (alternatively, variations in the prenatal

environment may be mirrored by changes in the postnatal environment). Understanding of the underlying mechanism is required before advocating intervention (see Chapter 1.2.1), because intervention studies to improve fetal and infant growth are likely to lead to only marginal reductions in the occurrence of adult chronic disease (or cognitive impairment) and may have adverse effects. For example, increased birth weight might cause an increase in Caesarean section rates and maternal obesity, and may be related to cancer of the prostate, breast and ovary in the offspring. Formula feeding to increase postnatal growth would decrease the health benefits of breast feeding (Joseph & Kramer, 2004). It may be that attention would be better focussed on the socioeconomic status of children throughout the world (Boyce & Keating, 2004).

6.2 Social class and cognitive ability

Much of the literature concerning developmental origins on health and disease has been concerned with whether birth weight is merely a surrogate for social class (Terry & Susser, 2001). Social class can be difficult to deal with in epidemiologic analyses as it can be measured and described in many different ways (Morris & Carstairs, 1991; Craig, 2001). Even standard scores such as the Register General's classification used here, can be classed as an ordinal or categorical variable, and therefore entered differently in regression analyses. In these analyses the Registrar General's classification could be entered in two ways:

1) Social class as a categorical variable (dummy variables created using social class V as the reference category). Social class I and II are combined due to small numbers.
2) Social class as an ordinal variable (as in Chapter 6.1). As ten births were classed as illegitimate (i.e. with no father recorded) these would be omitted from an ordinal classification of social class. Furthermore, this methodology is not established in the literature, and therefore the theory-based approach of dummy variables is used here. For further discussion see Shenkin, 2002 Chapter 5.3.5.

In this chapter the influence of social class at birth on cognitive ability is investigated. The hypotheses were that there would be an inverse relationship between social class and cognitive ability (i.e. more deprived children would score less well in adulthood), and also illegitimate children would perform less well.

6.2.1 Methods

The methods for recruitment, neuropsychological testing and archive data retrieval, including coding of social class, are described in Chapter 2.

6.2.2 Statistical analyses

Mean cognitive test scores are presented for each social class. The relationship between cognitive ability in old age and social class as an ordinal variable was investigated using Spearman's ρ. Multiple regression was used to investigate the influence of social class (coded as dummy variables for each social class including illegitimacy compared to reference class V) on *g*, RSPM and NART.

6.2.3 Results

Mean and SD for all cognitive test scores according to the social class of their father at birth is presented in Table 6.9, and illustrated in Figure 6.1 for RSPM, *g* and NART. Those in the most deprived social class or born illegitimately score generally less well than those in the higher social classes. In general, those adults born into the lowest (most deprived) social class scored worse on all cognitive tests (Spearman's ρ negative), with only NART reaching conventional statistical significance (ρ = -.21, P = .02) (Table 6.10).

Figure 6.1 Mean and 95% CI of social class at birth and (A) RSPM score, (B) *g*, (C) NART

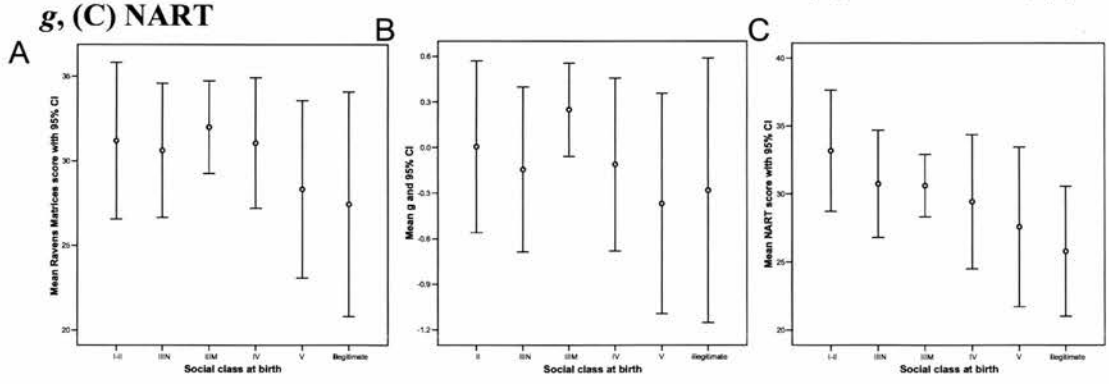


Table 6.9: Mean and SD of cognitive test scores by social class of father at birth

Social class	Max n	MMSE Mean	MMSE SD	RSPM Mean	RSPM SD	MHT Mean	MHT SD	VF Mean	VF SD	LM Mean	LM SD	*g* Mean	*g* SD	NART Mean	NART SD
I & II	11	28.9	0.9	31.2	6.5	58.9	6.3	34.6	13.5	33.4	15.0	.01	.79	33.2	6.6
IIIN	16	28.0	1.7	30.6	7.4	56.0	7.8	35.8	13.2	32.6	11.2	-.14	.98	30.7	7.4
IIIM	45	28.4	1.5	32.0	9.0	59.3	8.4	40.5	10.5	34.5	11.2	.25	.99	30.6	7.6
IV	16	28.4	1.3	31.1	7.3	58.3	10.0	33.5	11.4	29.2	12.8	-.11	1.03	29.4	9.3
V	12	28.1	0.8	28.3	8.2	53.0	10.0	38.4	16.0	30.0	9.3	-.37	1.14	27.6	9.2
Illeg	10	27.7	1.4	27.4	8.6	53.0	8.8	32.2	12.4	35.7	12.1	-.28	1.04	25.8	6.7

Table 6.10: Correlation between cognitive test scores and social class of father at birth (Spearman's ρ) (n = 110)

	MMSE ρ	MMSE P	RSPM ρ	RSPM P	MHT ρ	MHT P	VF ρ	VF P	LM ρ	LM P	*g* ρ	*g* P	NART ρ	NART P
Social class	-.13	.19	-.09	.36	-.11	.25	-.06	.55	-.06	.54	-.05	.60	**-.21**	**.02**

Bold type: P <.05

None of the multiple regression models relating social class to cognitive ability in older age were statistically significant. There was no contribution to RSPM, *g* or NART from any social class dummy variable (Tables 6.11, 6.12 and 6.13 respectively).

Table 6.11: Regression analysis of RSPM on social class (dummy variable compared to social class V) (n= 107)

	b	SE	beta	t	P	95% CI for *b*	
						Lower	Upper
Constant	28.3	2.4		11.9	.000	23.6	33.0
SC I or II	2.9	3.5	.10	.81	.42	-4.1	9.9
SC IIIN	2.3	3.1	.10	.73	.47	-3.9	8.5
SC IIIM	3.7	2.7	.22	1.4	.17	-1.6	9.0
SC IV	2.7	3.1	.12	.87	.39	-3.5	9.0
Illegitimate	-.89	3.6	.03	-.24	.81	-8.1	6.3

Residual SD = 8.0

R	R^2	Adj R^2	SEE	F	df regression	df residual	P
0.18	0.03	-0.014	8.2	0.71	5	101	0.62

Table 6.12: Regression analysis of *g* on social class (dummy variable compared to social class V) (n= 102)

	b	SE	beta	t	P	95% CI for *b*	
						Lower	Upper
Constant	-.37	.29		-1.28	.20	-.94	.20
SC I or II	.37	.43	.11	.88	.38	-.47	1.2
SC IIIN	.22	.39	.08	.58	.56	-.54	.99
SC IIIM	.62	.33	.31	1.89	.06	-.03	1.3
SC IV	.26	.39	.09	.67	.51	-.51	1.0
Illegitimate	.09	.46	.02	.19	.85	-.82	.99

Residual SD = 0.97

R	R^2	Adj R^2	SEE	F	df regression	df residual	P
0.231	0.053	0.004	0.998	1.08	5	96	0.37

Table 6.13 Regression analysis of NART on social class (dummy variable compared to social class V) (n= 110)

	b	SE	beta	t	P	95% CI for *b*	
						Lower	Upper
Constant	27.6	2.27		12.1	.000	23.07	32.09
SC I or II	5.60	3.29	.21	1.70	.09	-.92	12.12
SC IIIN	3.17	3.01	.14	1.05	.29	-2.80	9.13
SC IIIM	3.04	2.56	.19	1.19	.24	-2.03	8.11
SC IV	1.85	3.01	.08	.62	.54	-4.11	7.82
Illegitimate	-1.78	3.37	-.06	-.53	.60	-8.47	4.90

Residual SD = 7.6

R	R^2	Adj R^2	SEE	F	df regression	df residual	P
0.239	0.057	0.012	7.87	1.25	5	104	029

6.2.4 Discussion

There is a weak negative association between social class (father's occupation recorded at birth) and cognitive ability in childhood (estimated by the NART) with more deprived babies scoring less well. There is a trend in a negative direction between social class at birth and cognitive ability aged around age 80, but this does not reach conventional statistical significance. The correlation only reaches statistical significance for NART, an estimate of childhood ability. Multiple regression (using social class coded as dummy variables as compared to Social Class V) did not find a significant contribution to any cognitive test from social class at birth.

The finding of a significant association between social class and cognitive ability in childhood, but none in later life, is consistent with previous studies that have clearly shown that shared environment contributes moderately to cognitive ability in childhood (Richards et al., 2001), but to a much lesser extent in adulthood (Bouchard, Jr., 1998; Plomin, 1999). For example, in childhood, common environment contributes around a quarter of the variance in cognitive ability, whereas in (young) adulthood the contribution is close to zero (Bouchard, Jr., 1998).

The result from this cohort may be an artifact of the study methodology. Those who volunteered for this study are people born in Edinburgh hospitals who have survived into a healthy old age: there is a large selection bias, with those followed into old age

being different from the whole cohort born in hospital. As a volunteer group, they are generally of higher ability than the general population (mean NART 29.9 SD 7.9 equivalent to IQ 106, population mean IQ 100). It is likely that they are also of higher social class than the population: in the 1991 census the proportion of Edinburgh residents in social class I was 9.2%, II 30.9%, IIIN 26.7%, IIIM 15.2%, IV 10.3% and V 5.8% (UK Census Information Gateway, 2002). Very few participants in the Simpson's study were in social class IV or V in adulthood (Table 6.14). This restricted range may have masked a true association between social class and cognitive ability in older age.

The method used to code for social class is important, and varies between studies. We used social class as coded by father's occupation at the child's birth, but we also collected data on childhood social class (study participant's recall of their father's occupation) and adult social class coded by the highest occupation reached by the participant (or their husband for married women). Data available for this sample are from too few time points, and numbers are too small, to be able to assess the relative importance of socioeconomic change over time, but as can be seen from Table 6.14 the social class distribution changes with time. Those children whose births were coded as illegitimate and then adopted used their adoptive parent's occupation, as this would reflect the environment in which they lived. The ten illegitimate children moved into social class III. There is a substantial shift in this cohort in later life, with few people still in social class IV or V, and more in I or II.

Table 6.14 Participants in Simpson's study social class at birth, childhood and adulthood (n = 110)

	Birth		Childhood		Adulthood	
Social class	**n**	**%**	**n**	**%**	**n**	**%**
I	2	1.8	3	2.7	10	9.1
II	9	8.2	10	9.1	36	32.7
IIIN	16	14.5	21	19.1	20	18.2
IIIM	45	40.9	49	44.5	41	37.3
IV	16	14.5	15	13.6	1	.9
V	12	10.9	12	10.9	2	1.8
Illegitimate	10	9.1	0	0	-	-

Two studies illustrate the importance of the definition of social class. Firstly, a large, longitudinal, American study (n = 4,698) found an association between socioeconomic position (a composite of parental education, paternal occupation, and childhood financial status) and absolute level of cognitive function aged over 65 (beta = 0.034, P = .01), but not cognitive decline after mean 5.3 years (beta = -.003, P = .32) (Everson-Rose, Mendes de Leon, Bienias, Wilson, & Evans, 2003). This suggests that a better socioeconomic environment in earlier life has a small but significant effect on absolute level of cognitive function, but does not protect against cognitive decline. Secondly, however, in the Nurses' Health Study (n = 15,594), there was an association between educational achievement and cognitive function and decline (odds ratio of a score in the lowest 10% .49 (95% CI .36 to .66) if graduate degree), but little relationship between cognitive function or decline and other measures of socioeconomic status (husband's education, income, childhood socioeconomic status) (Lee, Kawachi, Berkman, & Grodstein, 2003). Studies examining social class have to be clear whether education, occupation or income is being used to define it, and also whether social class in childhood or adult life is being described. Here we use occupation to code social class: although we obtained data on educational attainment, we did not use this in the analysis. This cohort was leaving school just as the Second World War began, and the majority of participants left school at 14 regardless of ability, therefore there was little variance in educational attainment.

Social class is often discussed, particularly in epidemiological literature, as a confounder in the relationship between birth weight and outcome variables (e.g. hypertension, diabetes) (Kuh, Power, Blane, & Bartley, 2004b). Confounders must be related to the outcome but not be a cause of it, and be related to the risk factor, but not a consequence of it. In many cases, it may not be known whether or not a potential confounder is on the causal chain (Hennekens et al., 1987). Establishing whether or not a variable is part of a causal chain can be difficult, especially when the aetiology is likely to be multifactorial, as in cognitive ability. It is possible that some variables identified in the studies discussed here as potential confounders may

actually lie on the causal chain between birth weight and cognitive ability (i.e. mediate it); for example parental social class might affect fetal health through deprivation or smoking (Hack et al., 1992). This would mean that correcting for these so-called confounders would weaken or eliminate the association between birth weight and cognitive ability; but, rather than making the association irrelevant (which the term confounder can easily be taken to imply) it helps us to understand the mechanism of the association. In multivariate datasets in epidemiology one variable tends to be selected as the dependent and one as the independent variable and the rest are termed confounders, when in fact the interrelationships between these variables are likely to be more complex than this terminology implies. If it is unclear whether or not a covariate is a confounder, it is permissible to enter it into a multiple regression model and establish its impact on the relationship (Tabachnick, 2000). Statistical techniques more commonly used in psychological than medical journals such as path analysis and structural equation modelling can be useful in this situation, i.e. to identify mediators in a relationship as distinct from confounders (Batty, Gottfredson, & Deary, 2005; Singh-Manoux, 2005) but larger numbers and stronger associations than those found here are required (e.g. (Shenkin et al., 2001) combined epidemiological and structural equation modelling analyses to examine possible confounding and mediation in the birth weight-IQ association).

The finding of a small but significant relationship between social class and crystallised, but not fluid, cognitive ability in old age suggests that socioeconomic factors are important for cognition, but that their influence may change with time. This is been previously described in how shared environment effects change over the lifespan (Bouchard, Jr., 1998). In view of the biases within this cohort discussed above, this should be investigated further in other cohorts, preferably prospectively.

6.3 Apolipoprotein E

6.3.1 Introduction

Genetic influences account for over 50% of the variance in adult cognitive function (Plomin & Spinath, 2002), with multiple genes influencing such complex traits as "probabilistic propensities rather than predetermined programmes" (Plomin, 1999)

(p. C25). One gene which has been extensively studied in relation to various outcomes including cognitive function is Apolipoprotein E, (*APOE*) located on chromosome 19q31.2, in particular polymorphisms with the three alleles e2, e3 and e4. Frequencies vary between populations, and in Northern Europeans 75-80% carry e3, 15-20% e4, and less than 10% carry e2 (Eichner et al., 2002). *APOE*e4 carriers have a higher incidence of Alzheimer's dementia, early mortality, cardiovascular disease, and stroke than non-carriers (Smith, 2002). Heterozygote carriers of *APOE*e4 are at between 3 and 4 times increased risk of dementia of Alzheimer's type, and homozygotes have a 10 to 12 fold increase in risk (Farrer et al., 1997). This is a relatively small effect compared to genes which cause familial Alzheimer's dementia (APP, PSEN1, PSEN2, but variants in *APOE* are much commoner and therefore have a larger effect at a population level (Deary et al., 2004a). This has led to the study of the importance of *APOE* in normal cognitive ageing.

The literature in this area has provided mixed evidence, for example Anstey and Christensen (2000) reviewed ten studies of *APOE* and cognitive change and found five studies with an association, three studies that found it only for some tests, and two that did not find any influence of *APOE* on cognitive change. The effect of *APOE* seemed to be most reliable for tests of memory and processing speed (Anstey & Christensen, 2000). Inconsistent results may have been due to several factors including (1) limited statistical power (2) cognitive domain assessed and test used (3) age of participants (4) inclusion of preclinical dementia cases (Small et al., 2004).

This led to a meta-analysis of 38 studies published between January 1993 and February 2004 (Small et al., 2004). These studies included a total of 5,230 *APOE*e4 allele carriers and 15,535 non-carriers, with individual studies ranging from 22 to 5,299 subjects. Mean age ranged from 55.1 to 89.0 years. Various cognitive ability domains were assessed, and these were classified as Attention (e.g. trailmaking A); Executive Functioning (e.g. trailmaking B, Wisconsin card sorting test); episodic memory (e.g. Weschler Memory Scales); Global cognitive ability (e.g. MMSE, Moray House Test, AH4); Perceptual speed (e.g. digit symbol substitution, reaction time); Verbal Ability (e.g. verbal fluency tests, NART); Visuospatial Skill (e.g.

Raven's Progressive Matrices). The effect sizes were small (less than .10 of a standard deviation unit), but e4 allele carriers performed less well in specific cognitive domains, namely global cognitive functioning (28 studies, d = -.06, P <.01, 95% confidence intervals -.08 to -.04), episodic memory (24 studies, d = -.03, P <.05, 95% confidence intervals -.06 to -.01), and executive functioning (8 studies, d = -.09, P <.01, 95% confidence intervals -.13 to -.05).

There was significant heterogeneity of effect sizes, and the potential moderators of age, e4 and e2 zygosity were examined. Higher average age was associated with smaller group differences. Few studies had large enough numbers to allow the assessment of the importance of zygosity, but in those that did, homozygote e4 carriers performed less well in global ability and episodic memory. There was insufficient data to allow the influence of other potential moderators, e.g. sex, cardiovascular disease, diabetes, preclinical Alzheimer's disease.

Therefore, this study investigated the influence of *APOE*e4 allele carrier status on cognitive test performance, particularly the effect of *APOE*e4 allele carrier status on global cognitive functioning (*g*, MMSE, MHT) and episodic memory. None of the tests in this study were specific for executive functioning. The hypotheses were that there would be no difference between carriers and non-carriers in performance on crystallised ability (NART), but that carriers would perform less well on cognitive tests in later life, particularly in tests of memory. The interaction between *APOE*e4 and sex was investigated.

No previous studies have reported whether *APOE* genotype influences birth parameters. The relationship between *APOE* genotype and birth parameters was investigated in this cohort.

6.3.2 Methods

The methodology of recruitment and testing is described in Chapter 2. Methodology for cognitive testing is presented in Chapter 2.5 and for genotyping in Chapter 2.6.1 and Appendix 9.4.

6.3.3 Statistical analyses

Frequencies of *APOE* alleles are shown in Chapter 3.4, Table 3.6. For those with and without the *APOE*e4 allele mean (SD) cognitive test result is reported in older age for (1) crystallised ability (NART) i.e. estimate of earlier life ability (2) various cognitive tests (MMSE, RSPM, MHT, VF, logical memory, and *g*, a first unrotated component of more fluid-type abilities: see Chapter 3.2) i.e. ability in older age (3) cognitive change, estimated by correcting ability in old age for estimated prior ability using (i) *g* corrected for crystallised ability (NART) (ii) RSPM corrected for crystallised ability (NART) (iii) Logical Memory corrected for NART. Statistical significance for the difference between carrier and non carrier was tested using t-test (equal variance not assumed). Mean birth parameters for those with and without the *APOE*e4 are reported, and statistical significance for the difference between carrier and non carrier was tested using t-test (equal variance not assumed).

To determine effect sizes, and assess whether there was an interaction between *APOE*e4status and sex, a full-factorial general linear model was run with RSPM, Logical Memory and Verbal Fluency as dependent variables, with *APOE*e4 status and sex as fixed factors and NART as covariate.

6.3.4 Results

As hypothesised, there was no statistically significant difference between carriers of the *APOE*e4 allele and non-carriers in NART (mean difference 1.8, t = .64, P .53). Carriers performed less well in older age on the Logical Memory task (mean difference 5.6, t = -2.2, P = .03) but for no other test (Table 6.14).

Table 6.14 Mean cognitive test scores for carriers and non-carriers of *APOE*e4

Cognitive test	e4+ n	Mean	SD	e4- n	Mean	SD	Mean diff	t	df	P
NART	34	28.2	1.4	71	31.0	7.6	1.8	.64	103	.53
MMSE	32	28.5	1.1	70	28.2	1.4	-.3	1.0	100	.28
RSPM	32	29.1	7.0	70	31.5	8.6	2.4	-1.5	100	.13
MHT	31	58.3	7.7	68	57.2	8.8	-.9	.66	97	.51
VF	34	39.2	11.9	71	36.5	12.6	-2.7	1.0	103	.31
LM	33	28.9	12.7	71	34.5	11.0	**5.6**	**-2.2**	**102**	**.03**
g	29	-.07	.85	68	.04	1.0	.11	-.61	95	.54

Bold type: P < .05

If general cognitive ability (*g*), non-verbal reasoning (RSPM) and logical memory are corrected for prior ability (NART), *APOE*e4 carriers perform less well on logical memory (t (102) = -2.5; P = .013) and there is a trend towards poorer performance for carriers for both *g* and RSPM (Table 6.15).

Table 6.15 Mean 'cognitive change' for carriers and non-carriers of *APOE*e4

'Cognitive change'	e4+ n	Mean	SD	e4- n	Mean	SD	Mean diff	t	df	P
***g* corr NART**	30	-.08	.89	68	.14	.94	-.22	-1.1	96	.28
RSPM corr NART	33	-.15	.90	70	.14	.98	-.29	-1.5	101	.14
LM corr NART	33	-.38	1.09	71	-.14	.92	**-.52**	**-2.5**	**102**	**.01**

In the general linear model there were significant multivariate effects (Wilk's lambda) of *APOE*e4allele status F(3,94) = 3. 67, P = .015, η^2 = .105; prior IQ (NART): F(3,94) = 12.76, P = <.001, η^2 = .289 and sex F(3,94) = 2.74, P = .048, η^2 = .080. *APOE*e4 status contributed significantly to Logical Memory F(1,96) = 7.44, P =.008, η^2 = .072, but not verbal fluency F(1,96) = 3.10, P = .08, η^2 = .031 or Raven's F(1,96) = .37, P = .54, η^2 = .004. Sex contributed significantly to RSPM F(1,96) = 7.9, P = .006, η^2 = .076 (men scored higher) but not Logical Memory or Verbal Fluency. There was no significant sex*carrier interaction. NART contributed significantly to all three cognitive outcomes: Logical Memory F(1,96) = 4.80, P = .03, η^2 = .048; verbal fluency: F(1,96) = 25.44, P = <.001, η^2 = .209; RSPM F(1,96) = 14.09, P = <.001, η^2 = .128.

There were no statistically significant differences between carriers of the *APOE*e4 allele and non-carriers in any birth parameter (Table 6.16).

Table 6.16 Mean birth parameters for carriers and non-carriers of *APOE*e4

	e4+ n	Mean	SD	e4- n	Mean	SD	t	df	P
BW (g)	34	3326.1	525.8	71	3341.6	413.9	-.15	100	.88
BL (cm)	32	50.8	2.7	70	50.7	2.7	.22	100	.82
PW (g)	24	714.0	158.6	54	665.1	140.0	1.3	76	.20

BW = birth weight BL = birth length PW = placental weight

6.3.5 Discussion

In this study of community dwelling older volunteers carriage of the *APOE*e4 allele did not influence performance on crystallised ability (i.e. estimate of prior ability), as hypothesised. *APOE*e4 carriers performed less well on the logical memory test, but on no other test in old age. Carriers performed less well on logical memory once prior ability was considered, and there was a trend towards carriers suffering more decline in general and non-verbal abilities. There was no influence of *APOE* genotype on birth parameters.

This is consistent with previous literature which has shown that the presence of *APOE*e4 did not influence early life ability. For example in the LBC 1921 study (Deary et al., 2003a) found no significant difference in performance on the Moray House Test between carriers and non-carriers at age 11 (n = 466; P = .36) It should be noted that 31 subjects included in the Simpson's study were also included in the LBC 1921 study. A study of 97 high-*g* children and 98 controls also found no association between *APOE* genotype and general cognitive ability (*g*) (Turic, Fisher, Plomin, & Owen, 2001).

In older age we found an association between *APOE*e4 carriage and logical memory, with carriers performing less well. This is the cognitive domain most consistently identified as associated with *APOE* genotype in the literature (Small et al., 2004; Anstey et al., 2000), and was the cognitive domain identified as associated with *APOE* genotype in other studies from our research group. For example, in the LBC 1921 study (Deary et al., 2004a) carriers of *APOE*e4 scored less well than non-carriers on the Weschler memory test (n = 462), but there was no difference in performance for tests of non-verbal reasoning or verbal fluency. 31 subjects in this study were included in the current analyses. In 466 people who re-sat the Moray House Test almost 70 years after taking part in the Scottish Mental Survey 1932, e4 carriers scored significantly less well on the MHT (mean difference 4 points, P = .009) than non-carriers, but we did not replicate this finding (Deary et al., 2003a).

The effect size of a mean difference between carriers and non-carriers of 5.6 points on logical memory (.4 to .5 SD) or 7.2% of the variance is higher than that found in similar studies (e.g. *APOE* status accounted for about 4% of the variance on memory scores in Deary et al., 2004a, and the meta-analysis found the mean effect size to be less than .10 standard deviation units (Small et al., 2004)). Our increased effect size may be due to the restricted range in this cohort with more specific inclusion criteria.

The increasing evidence that Logical Memory shows a more consistent association with *APOE*e4 than fluid intelligence has led to speculation that there may be substantial ageing effects on the cognitive domain of memory that are not shared with ageing effects on general cognition (Salthouse et al., 2003).

Cognitive decline was estimated in this study by correcting general cognitive ability (*g*), non-verbal reasoning (Raven's) and logical memory for prior ability (NART). *APOE*e4 carriers showed more 'decline' on logical memory ($t(102) = -2.5$; $P = .013$) and there was a trend towards more 'decline' for e4 carriers for both *g* and RSPM. The majority of data in this study were cross-sectional, as are most studies of cognitive ability and *APOE*, however our study used an estimate of prior ability that has been validated as a measure of childhood IQ (Deary et al., 2000). Despite this validity, there will still be a difference between an estimate of prior ability and the actual measured ability. The results in this study are, however, consistent with prospective studies, which have shown greater cognitive decline among *APOE*e4 carriers (e.g. Deary et al., 2004a; Bretsky, Guralnik, Launer, Albert, & Seeman, 2003). By using RSPM or *g* corrected for NART to estimate cognitive change we avoided the ceiling effect of some cognitive tests e.g. MMSE. Also, we do not have any data on cognitive abilities at other time points, and are therefore unable to estimate the trajectory of change.

It is possible that some participants in the Simpson's study may be developing mild cognitive impairment or dementia, and *APOE* may play a different role in those undergoing 'normal' versus 'pathological' ageing. In the absence of longitudinal follow-up this point cannot be refuted, although all our participants scored >= 24 on

MMSE and were living independently in the community with no history of dementia. If the analyses are repeated including only those with MMSE >=28, *APOE*e4 carriage is no longer associated with poorer logical memory (mean score e4+ 29.7 (n = 27, SD 12.1), e4- 29.7 (n = 47, SD 12.1) t = .76, df 72, P = .11). The lack of statistical significance may be due to the reduced power as the numbers decrease, but the possibility of preclinical disease cannot be excluded. However, this may be overly stringent, because MMSE also includes memory, and excluding low MMSE scorers from analyses including Logical Memory effectively removes memory variance from a memory test.

Cognitive change in older age is associated with the accumulation of vascular pathology (Hachinski & Munoz, 2000), and therefore genes that influence both cardiovascular risk and cognition are of interest. *APOE* genotype has also been associated with cardiovascular disease, with *APOE*e4 being associated with higher cholesterol levels and carotid atheroma, accounting for 5-8% of the variance in atheroma detected on ultrasound or post-mortem (Eichner et al., 2002). Possession of *APOE*e4 may therefore modulate both cardiovascular disease and cognitive change. Birth weight has been related to risk factors for cardiovascular disease (Barker, 1999), with a decrease in risk of cardiovascular disease of around 20% for each kilogram increase in birth weight (Rich-Edwards, 2004). Because both *APOE* and birth parameters (especially weight) have each been related to both cardiovascular disease and cognition, we investigated whether *APOE* was related to birth parameters, and found no relationship. This may be due to the small sample in this study, unable to detect the expected small effect size. Alternatively, *APOE* could exert its influence later in life, possibly interacting with birth weight. Studies of fetal programming have started to consider the importance of genetic as well as environmental influences, but mostly have used studies of twins or comparisons of parents and offspring (Kuh et al., 2003) (p. 452).

The finding of an association between *APOE*e4 and memory in normal cognitive ageing has led to more mechanistic studies to try to account for this effect. Smaller hippocampal volumes in *APOE*e4 carriers (Cohen, Small, Lalonde, Friz, &

Sunderland, 2001) may account for the difference in performance in memory tests, as the hippocampal formation is integral to episodic memory performance (Nyberg, McIntosh, Houle, Nilsson, & Tulving, 1996). Presence of *APOE*e4 is associated with an increase in Alzheimer's disease pathology (Farrer et al., 1997), and also microvascular changes in the brains of patients with Alzheimer's disease (Yip et al., 2005). Other neuronal pathologies have been proposed as underlying cognitive damage, such as the possession of the *APOE*e4 allele affecting the protection and repair of neuronal cells, meaning that any damage is more likely to lead to neurodegeneration (Mahley & Rall, Jr., 2000). Advances in technology have made screening for genes implicated in various outcomes (e.g. cognition, cardiovascular disease) much less labour intensive and costly, and this means that epidemiological studies of programming can also include genotyping, and investigate the interactions between genetic and environmental influences. This, in conjunction with mechanistic studies of the influence of these genes, may identify targets to affect age-related cognitive change.

7 Contribution of early life factors to cerebrovascular disease

In this chapter the contribution of various early life factors to cerebrovascular disease (CVD) around age 80 is considered at several levels. First, the relationship between birth parameters (weight, but also length and placental weight) and CVD is considered using the outcome measures of 1) self-report of cerebrovascular disease and 2) vascular risk factors (particularly markers of atheromatous load: ABPI, carotid artery stenosis and intima media thickness (IMT)). Secondly, the relationship between birth parameters and brain MRI features of CVD (WML and DTI parameters) is investigated. Thirdly, the relationship between social class and CVD is reported at three levels 1) self-report of CVD 2) markers of atheroma and 3) neuroimaging features of CVD. Finally, the relationship between *APOE* genotype and 1) markers of atheroma and 2) neuroimaging features of CVD are investigated.

7.1 Birth parameters and cerebrovascular disease

7.1.1 Introduction

As reviewed in Chapter 1.2.2, epidemiological studies have found a robust association between birth weight and stroke mortality (Martyn et al., 1996; Leon et al., 1998) and morbidity (Hypponen et al., 2001; Eriksson et al., 2000; Rich-Edwards et al., 1997; Rich-Edwards, 2004; Rich-Edwards et al., 2005). Some studies have suggested the association may be stronger for haemorrhagic stroke (Hypponen et al., 2001; Rich-Edwards et al., 2005), but others have not replicated this (see Rich-Edwards et al., 2005). These studies have variously been criticised for loss to follow-up, use of self-reported birth weight, use of either fatal or non-fatal end points, failure to adjust for socio-economic status or lifestyle risk factors (Rich-Edwards, 2004). However, individual studies within this group have dealt with these criticisms, and collectively the epidemiological evidence shows that decreased birth weight does appear to increase the risk of stroke. This relationship is, however, less strong than for coronary heart disease.

The relationship between birth weight and stroke may be due to (mediated by) a relationship between birth weight and cardiovascular risk factors (e.g. blood pressure

(Huxley et al., 2000), cholesterol (Owen et al., 2003), diabetes (Rich-Edwards et al., 1997)). However, studies that adjust for cardiovascular risk factors find that these factors do not explain the association of birth weight with cardiovascular disease (Koupilova et al., 1999; Rich-Edwards et al., 1997; Rich-Edwards, 2004).
There is therefore a need for studies to examine the relationship between birth parameters and cerebrovascular endpoints which are more sensitive than presence or absence of stroke – none were found on a review of the literature. Examples of these are WML and changes in white matter tract integrity (using DTI). It is important that vascular risk factors are also taken into account, and this can be done by measuring the common endpoint of vascular risk factors, atheroma (Bots et al., 1993; Bots et al., 1997). In this study, two non-invasive measures of atheromatous load were used: in the lower limb, the ankle-brachial pressure index (ABPI) (Fowkes, 1991); in extracranial carotid arteries using duplex ultrasonography (Grobbee et al., 1994) assessing proportion of the lumen occluded (% stenosis), or intima-media thickness (IMT) in the common carotid artery. ABPI, carotid artery stenosis and carotid IMT have all been associated with cerebrovascular events and WML on MRI scans (Bots et al., 1997; Bots et al., 1993). Previous studies have suggested no relationship between birth weight and ABPI (Martyn et al., 1998), but found conflicting results for any influence of birth weight on carotid artery stenosis or IMT, suggesting a possible relationship but mainly accounted for by later social class and biological vascular risk factors (Martyn et al., 1998; Lamont et al., 2000; Gale et al., 2004; Tilling et al., 2004).

The relationship between birth parameters (particularly birth weight) and cerebrovascular disease in the Simpson's cohort were investigated at three levels (1) self-report of vascular disease (2) vascular risk factors (particularly ABPI and IMT) (3) MRI features of cerebrovascular disease (WML and DTI).

The hypotheses were that (1) lower birth weight would be associated with an increased incidence of vascular disease (2) lower birth weight would be associated with vascular risk factors, i.e. lower ABPI and higher IMT (3) lower birth weight

would be associated with increased evidence of cerebrovascular disease, i.e. increased WML load and <D>, decreased FA.

7.1.2 Methods

The methods for recruitment, data collection and archive retrieval are described in Chapter 2. Incidence of vascular disease was self reported on direct questioning as to any doctor's previous diagnosis of stroke, TIA or 'mini-stroke', heart attack, angina, peripheral vascular disease, or other vascular problems. All carotid ultrasonography was performed by Mrs Elizabeth Eadie or Prof Joanna Wardlaw, measuring maximal % stenosis, intima-media and intima-adventitia thickness of the distal common carotid artery. For details, see Appendix 9.5. Maximal carotid artery stenosis was estimated as percentage of lumen diameter lost on each side, and the maximum degree of stenosis on either side recorded as 0-20%, 21-40%, 41-60%, 61-80%, 81-99%, 100%. Carotid intima media thickness is the mean of measures on the two sides (right and left).

7.1.3 Statistical methods

Descriptive statistics are presented for those with and without a history of cerebrovascular disease and other vascular risk factors. Differences in birth parameters between those with and without a history of vascular risk were assessed using t-test (equal variance assumed unless Levene's test $P < .05$). Forward stepwise logistic regression was used to determine which variables predicted CVD. The association between continuous risk factor variables (e.g. blood pressure, HbA_{1c}) and birth parameters was investigated using Pearson's correlation (r).
Two outliers with ABPI much greater than 1.25 were recoded as ABPI 1.25 to avoid their having undue influence on the results.

7.1.4 Results

7.1.4.1 Birth parameters and cerebrovascular disease

Of 110 subjects in the Simpson's study, 11 (10%) reported a doctor's diagnosis of stroke or TIA (see Table 3.1). 37 (33.6%) reported cardiovascular disease, 6 (5.5%) other vascular disease (5 intermittent claudication due to peripheral vascular disease, one abdominal aortic aneurysm), 49 (44.5%) hypertension, 7 (6.4%) diabetes (2 diet controlled, 2 oral hypoglycaemics, 2 insulin treated type II).

Descriptive statistics are shown in Table 7.1. There was no difference in age between those with or without a history of CVD (t = .02, df 108, P = .98) and no statistically significant difference in sex distribution (male 12.1% CVD+, female 9.1% CVD+; X^2 = .24; P = .73). Those with a history of cerebrovascular disease scored less well on the MMSE (mean difference -1.0 points; t = -2.23, df 105, P = .03) but no other cognitive test. There were no differences between those with or without a history of CVD for birth weight (t = -1.2, df 108, P = .22), or birth length (t = -.86, df 105, P = .39), but placental weight was significantly lower in those with a history of CVD (mean difference -102.3g; t = -2.2, df 81, P = .036).

Table 7.1 Descriptive statistics for those with and without a history of CVD

	CVD+			**CVD-**			**Mean**		
	n	**Mean**	**SD**	**n**	**Mean**	**SD**	**diff**	**t**	**P**
Age (yrs)	11	78.4	1.6	99	78.4	1.5	0	.02	.98
Cognitive test									
MMSE	10	27.4	1.8	97	28.4	1.3	**-1.0**	**-2.2**	**.03**
NART	11	26.5	7.6	99	30.3	7.9	-3.8	-1.5	.13
RSPM	10	28.8	8.6	97	31.0	8.1	-.8	105	.42
VF	11	30.8	12.3	99	38.0	12.2	-7.2	-1.8	.07
LM	11	30.2	9.3	98	33.2	11.9	-3.0	-.8	.42
Birth parameter									
BW (g)	11	3173.1	311.8	99	3351.4	468.3	-178.4	-1.2	.22
BL (cm)	11	50.0	3.1	96	50.7	2.7	-7.5	-.9	.39
PW (g)	10	588.3	100.0	73	690.6	146.3	**-102.3**	**-2.2**	**.036**

CVD+ = history of cerebrovascular disease
CVD- = no history of cerebrovascular disease

Placental weight was converted to kilograms, and forward stepwise logistic regression including only placental weight showed an increased risk of CVD of 0.4% (95% CI 0 to 84%, P = .043) per kg increase in placental weight (Table 7.2). If other potential contributory birth characteristics (birth weight, length, pregnancy number, maternal age, sex) are added, the model remains unchanged with only placental weight predicting history of CVD (B = -.5.5, SE 2.7, P = .043, exp (B) .004 (95% CI .00 to .84)). If gestational age is added to the model none of the variables contribute significantly.

Table 7.2: Forward stepwise logistic regression of placental weight (kg) on cerebrovascular disease incidence (n = 83)

	B	SE	Exp(B)	P	95% CI for *b*		R^2
					Lower	Upper	
Constant	1.5	1.7	4.6	.36			
Placental Weight	-5.5	2.7	.004	.04	.00	.84	0.11

7.1.4.2 Birth parameters and vascular risk factors

Descriptive statistics for birth parameters of those with and without a history of cardiovascular disease and hypertension are shown in Table 7.3. Due to the small numbers of those with a reported history of diabetes (n = 7) and peripheral vascular disease (n = 6) and the possibility of misclassification, these are not reported here. There were no consistent associations between cardiovascular or hypertension history and birth parameters. Those with a history of hypertension were shorter at birth than those without a history of hypertension (mean difference -1.2cm; t -2.3, df 105, P = .02).

Table 7.3 Mean birth weight parameters for those with and without a history of vascular risk factors (cardiovascular disease, hypertension) (n = 110)

CaVD	**n+ CaVD+**	**Mean**	**SD**	**n- CaVD-**	**Mean**	**SD**	**Mean diff**	**t**	**df**	**P**
BW (g)	37	3383.3	443.6	73	3308.4	464.8	74.9	.81	108	.42
BL (cm)	35	50.8	2.9	72	50.6	2.7	.20	.36	105	.72
PW (g)	24	686.0	122.7	59	675.1	154.0	10.8	.34	53 [a]	.74
Ht	**Ht+**			**Ht-**						
BW (g)	49	3255.2	435.0	61	3396.6	468.3	-141.4	-1.6	108	.11
BL (cm)	48	50.0	2.6	59	51.2	2.7	**-1.2**	**-2.3**	**105**	**.02**
PW (g)	38	658.0	144.0	45	695.4	145.2	-37.5	-1.18	81	.24

[a] Equal variance not assumed (Levene's test P <.05)
Bold type: P <.05
CaVD = cardiovascular disease Ht = hypertension
+ = history of the disease - = no history of the disease

Bivariate correlations among vascular risk factors are shown in table 7.4. Elevated vascular risk would be expected with higher SBP, DBP, IMT, HbA_{1c}, cholesterol, fibrinogen and BMI, but lower ABPI. In general, correlations among vascular risk factors are in the expected direction (e.g. high systolic blood pressure associated with

higher carotid IMT and cholesterol, and lower ABPI), but there was no significant association with HbA_{1c}, fibrinogen or BMI. The lack of substantial inter-correlations means that each risk factor should be examined individually.

Table 7.4 Correlation matrix of vascular risk factors (Pearson's r) n = 104 to 110 (see Table 3.5)

Test	SBP	DBP	ABPI	IMT	HbA_{1c}	Chol	Fib
DBP	.08	-	-	-	-	-	-
ABPI	**-.22**	-.02	-	-	-	-	-
IMT	**.23**	.12	-.11	-	-	-	-
HbA_{1c}	-.01	-.15	-.09	.01	-	-	-
Chol	**.25***	**.25***	.01	-.01	.01	-	-
Fib	.04	-.10	-.08	-.13	.12	.05	-
BMI	.01	.16	**.20**	-.08	.09	-.04	.03

Bold type: P <.05 * P <.01

This chapter focuses on the vascular risk factors of ABPI and carotid artery atherosclerosis (% stenosis and IMT) which are markers for atheromatous load. The mean (SD) values for ABPI and IMT for categories of birth weight are presented in table 7.5. There is a suggestion of a decrease in IMT as birth weight increases, but no clear pattern for ABPI. Boxplots illustrating the relationship between birth weight and both ABPI and IMT are shown in Appendix 9.11.

Table 7.5 Vascular risk factors (ABPI and IMT) by birth weight divided into categories

	ABPI			IMT		
Birth weight	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**
<2500g	3	1.04	.04	3	1.12	.08
2501-3000g	22	.86	.18	23	.91	.13
3001-3500g	43	.94	.18	43	.90	.16
3501-4000g	34	.90	.19	34	.98	.24
>4000g	7	.81	.23	7	.83	.11

Mean birth weight for each category of carotid artery stenosis (as estimated by the ultrasonographer) is shown in Table 7.6.

Table 7.6 Birth parameters by maximal carotid artery stenosis

	Birth weight (g)			Birth length (cm)			Placental weight (g)		
Stenosis	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**
0-20%	62	3329.4	472.9	60	50.7	2.9	48	682.4	151.2
21-40%	29	3313.4	469.3	28	51.0	2.6	19	691.7	125.9
41-60%	8	3455.2	538.7	8	50.6	2.4	7	730.9	157.3
61-80%	7	3376.9	317.0	7	49.8	2.9	6	592.8	128.3
>80%	4	3226.7	222.3	4	49.1	1.5	3	575.7	129.9

The correlation between birth parameters and ABPI and IMT are presented in Table 7.7, showing both parametric (Pearson's r) and non-parametric (Spearman's ρ) coefficients, in view of the lack of a clear linear relationship. Scatterplots for all birth parameters and both ABPI and IMT are shown in Appendix 9.11. Birth weight is presented both raw, and corrected for gestational age (linear regression, birth weight as dependent variable, gestational age as independent variable, saving standardised residuals). Birth length and placental weight, and their relationship with ABPI and IMT, are also presented.

Table 7.7: Correlation between birth parameters and vascular risk factors (ABPI and IMT)

	ABPI		IMT		ABPI		IMT	
	r	**P**	**r**	**P**	**ρ**	**P**	**ρ**	**P**
Hypothesis	+		-		+		-	
Birth weight (n=110)	-.08	.43	.01	.89	-.07	.45	.03	.77
BW corr for GA (n=100)	-.06	.58	.03	.74	-.05	.65	.05	.58
Birth length (n=107)	-.04	.65	-.07	.47	-.03	.75	-.08	.40
Placenta weight (n = 83)	-.03	.82	-.04	.65	.03	.77	.03	.78

There is no statistically significant relationship between any birth parameter and ABPI or IMT. In view of this, the influence of other vascular risk factors or potential confounders, such as social class or biological vascular risk factors, is not further considered here.

7.1.5 Discussion

In this cohort there was a small but statistically significant increase in self-reported stroke/TIA incidence with increasing placental weight (0.4% per kg) but with no other birth parameter. Once gestational age was added to the model placental weight was no longer a significant predictor of CVD.
There was no association between the degree of atherosclerotic narrowing in peripheral or carotid arteries and birth weight, length or placental weight.

This study is considerably smaller than other studies of cerebrovascular disease incidence, and the results should be treated with caution. The absence of a relationship between birth weight and cerebrovascular disease history may be due to inadequate power to detect an effect, with only 11 (10%) people reporting a history of stroke or TIA. In addition, the use of self-report to define cerebrovascular disease raises the possibility of misclassification bias. This is likely because, of the 11 people who reported a stroke, only 4 had a definite infarct on MRI imaging, and a further 2 had primary intracerebral haemorrhage. 8 were taking aspirin, one warfarin, and of the two not on aspirin or warfarin, one had intracranial haemorrhage on the MRI. The one remaining patient (not taking warfarin or aspirin), although they gave a history of stroke, clinically appeared to have a Bell's palsy. However, as stroke is primarily a clinical diagnosis, the self-report outcome rather than the neuroimaging is used. The numbers in this cohort were too small to analyse the data separately for cerebral infarcts and haemorrhages, and the large epidemiological studies published (Rich-Edwards et al., 2005; Hypponen et al., 2001; Martyn et al., 1996) are best placed to assess the relative influence of early life parameters and confounders on stroke incidence.

The effect size of the influence of placental weight on stroke incidence is very small, with wide confidence intervals, and may be due to chance or bias. However, one previous study (n = 13,249) found an association between placental size and mortality from stroke (Martyn et al., 1996). Birth weight was the strongest predictor of stroke mortality, but those with relatively large heads and small placentas had an increased mortality. These proportions were related to the mother's pelvic shape: a

flat bony pelvis predicting risk of stroke. The authors therefore suggested that maternal poor nutrition in her own childhood affected her pelvic growth and thus her ability to sustain normal placental and fetal growth, contributing to increased stroke incidence. One summary report (Lawlor, Ben-Shlomo, & Leon, 2004) suggested that a larger study of 15,000 births (Leon, 1998) did not find an association between placental weight and stroke incidence, but these data were not included in the original paper (Leon et al., 1998). Placental weight has been used as a crude measure of placental function, but placental weight is particularly prone to measurement error (Hargitai et al., 2004). Few studies of the developmental origins hypothesis include data on placental size. Studies which are interested in prenatal influences should, where data exist, consider the importance of the placenta as the route by which nutrients and hormones affect the developing fetus (Gagnon, 2003).

The inclusion of gestational age in the model predicting stroke incidence in the Simpson's study eliminated the relationship between placental weight and cerebrovascular disease. Previous studies have suggested that length of gestation rather than birth size may be important in predicting mortality from occlusive stroke (Koupil, Leon, & Lithell, 2005), but there is a large risk of misclassification of gestational age in historical studies relying on maternal report of last menstrual period.

In view of the possibility of misclassification bias in the history of stroke, and the small sample size, this study used two non-invasive measures of atheromatous load as sensitive measures of cerebrovascular disease risk, namely ABPI and carotid stenosis and IMT. Our finding of no relationship between birth weight, length or placental weight and ABPI is consistent with the only other published study found in the literature. In an elderly cohort (mean age around 68 years) in Sheffield (Martyn et al., 1998), 186 subjects underwent ABPI. There was no significant association between ABPI and birth weight (P for trend .36) or any other birth measure (including birth length and placental weight), although mean birth weight was lowest in people with the lowest ABPI.

Several studies have examined the relationship between birth parameters and carotid atherosclerosis (% stenosis or IMT). These have had conflicting results (see Chapter 1.2.2). For carotid stenosis, one study in Sheffield found lower birth weight associated with increased atherosclerosis in 181 subjects mean age 68 years (Martyn et al., 1998) and another study of 389 subjects, mean age 70 years, found a non-significant trend in this direction (Gale et al., 2002). Studies including IMT are larger, but include younger subjects, and have had conflicting results. The largest, Atherosclerosis Risk in Communities (ARIC) study, had 9,817 participants (aged 44-65) and found a weak *positive* association between recalled birth weight and IMT, attenuated after adjustment for sex, socioeconomic class and cardiovascular risk factors (Tilling et al., 2004). A study of 750 Dutch men and women aged 28 years (Oren et al., 2004) examined 750 and found no overall relationship between IMT and birth weight. However, those with low birth weight who showed exaggerated postnatal growth had a significant association with CIMT. The Newcastle thousand families study (Lamont et al., 2000) studied 347 subjects (44.4% men) aged 49-51 years and found a weak negative association between birth weight and IMT for men only, attenuated by correction for adult socioeconomic position and lifestyle. Once other biological risk factors were included in the analyses (particularly waist-hip ratio and smoking) birth weight did not contribute independently. Gale et al. (2002) found that in 181 subjects with mean age 70.0 (SD 2.2), there was a negative association between birth weight and IMT in women, but this was non-significant once gestational age and cardiovascular risk factors were considered. For men, there was again a surprising suggestion of a *positive* association (Gale et al., 2002). These studies suggest that adult lifestyle and biological risk markers are more important determinants of cardiovascular health than birth parameters.

Our study is smaller than those described above, and therefore the results should be treated with caution, as our non-significant results may be type II error. However, the effect size of the correlation coefficients was small (.03 to .08). Post hoc power calculations show that with 105 participants an effect size of .28 would be statistically significant ($P < .05$) with 90% power, and .24 with 80% power (UCLA department of statistics, 2005). Therefore a correlation effect size up to around .25

would not reach statistical significance in this study, but could be clinically significant.

Our participants are significantly older than the other studies, and therefore likely to have a higher burden of atheromatous change. This gains some support when the mean IMT of .70mm (SD.17) (Tilling et al., 2004) is compared with the Simpson's study mean of .94 mm (SD.18). In the absence of a significant relationship the relative importance of other vascular risk factors and potential confounders was not assessed here. Although there is some suggestion of a sex difference in the previous studies described above this was not investigated here due to the lack of power, and the resultant increase in multiple testing.

This study therefore adds to the evidence that there is no simple causal pathway from an adverse intrauterine environment to increased incidence of vascular risk factors, to increased atherosclerosis, to cerebrovascular disease (Gale et al., 2002). Early life influences may be important in the conversion of atherosclerosis to atherothrombosis. Associations between early life parameters and cerebrovascular outcomes may be confounded by later life vascular risk. Future epidemiological studies require large numbers at different ages, taking account of potential confounders at different stages in the life course. There is a need for methodological studies to elucidate the relationships among early life and other vascular risk factors, atherosclerosis and clinical outcomes.

7.2 Birth parameters and brain imaging

7.2.1 Introduction

Chapter 7.1 dealt with the relationship between birth parameters and CVD using self-report of CVD and measures of atherosclerosis. In this section, early life influences on brain imaging markers of cerebrovascular disease are considered. White matter lesions (WML) are areas of high signal on T2- and proton density weighted MR images, and are commonly separated into patchy deep white matter hyperintensities (DWMH) and smooth periventricular hyperintensities (PVH) (see Chapter 1.1.2.2, Figure 1.2). WML are thought to have an ischaemic aetiology, with some studies

suggesting that DWMH probably have a vascular origin (Schmidt et al., 1993; Schmidt et al., 2004) whereas PVH may be due to disruption of the ependymal lining with subependymal gliosis and myelin degradation (Leaper et al., 2001; Schmidt et al., 2004). WML are associated with stroke and TIA (Longstreth, Jr. et al., 1996; Vermeer et al., 2003a), and can be seen as a non-specific marker for CVD, and DWMH may be more strongly associated with CVD than PVH (Schmidt et al., 2004). We therefore hypothesised that there would be a negative association between birth weight and WML load, stronger for DWMH (i.e. lower birth weight associated with increased WML).

WML are multifactorial and crudely measured, and there is a need for more sensitive measures of white matter tract damage. Diffusion tension imaging (DTI) (Basser et al., 1994) measures the diffusion of water molecules on a voxel by voxel basis (for more detail see Chapter 5.1). By using tensors - a mathematical construct used to describe multi-dimensional vector systems - to describe the restriction of proton diffusion by white matter tracts, DTI allows examination of the tissue microstructure (Le Bihan, 2003; Sullivan et al., 2003). Two parameters are commonly computed to quantify the diffusion. **Mean diffusivity** (<D>) indicates the magnitude of water molecule diffusion in any direction (with the effect of anisotropy removed), whereas **fractional anisotropy** (FA) measures the coherence and orientation of diffusion (Basser et al., 1996; Pierpaoli et al., 1996). In white matter tracts, water movement is restricted by axonal membranes and myelin, therefore areas containing intact neurones would be expected to have a low <D>, and high FA. In stroke disease, <D> falls and FA rises acutely, but in chronic stroke lesions <D> is relatively high and FA low (Sotak, 2002; LeBihan et al., 2001).We therefore hypothesised that birth weight would be negatively associated with <D> and positively associated with FA (i.e. higher birth weight associated with white matter tract integrity). In view of the weak association between placental weight and stroke history found above (Chapter 7.1.4) we further hypothesised that placental weight would be negatively associated with <D> and positively associated with FA.

7.2.2 Methods

The methods for recruitment and neuropsychological testing are presented in Chapter 2. The scan acquisition MRI protocol is described in Chapter 2.8.2 and Appendix 9.6. In brief, a standard structural brain MRI protocol was followed, comprising (1) sagittal T1-weighted spin-echo (2) axial T2-weighted fast spin-echo (FSE) (3) axial fluid attenuated inversion recovery (FLAIR) (4) axial T2* gradient echo , and (5) three-dimensional fast spoiled gradient echo T1 weighted volume sequence (inversion recovery prepared) with whole brain coverage

WML: Details of the methods used to rate the WML are given in Chapter 4.2.2 and Appendix 9.6.3. The T-2 weighted MRI images were analysed for WML by an experienced neuroradiologist (Professor J Wardlaw) blind to all other data. Several rating scales were used, but the Fazekas scale (Fazekas et al., 1987) has proved to be the most reliable, and will be presented here. DWMH and PVH are rated separately on a four point scale (0-3) (see Figure 4.2).

DTI: Details of the DTI protocol are given in Chapter 5.2 and Appendix 9.7.1. Briefly, data acquisition for DTI was based on spin-echo echo-planar (EP) imaging (Shenkin et al., 2003). Sets of axial EP images (b = 0 and 1000 s/mm^2) were collected with diffusion gradients applied sequentially along six non-collinear directions. Five acquisitions consisting of a baseline T_2-weighted EP image and six diffusion-weighted EP images, a total of 35 EP images, were collected per slice position. From the DTI data, the apparent diffusion tensor of water (**D**) was calculated in each voxel from the signal intensities in the component EP images (Basser et al., 1996). Maps of <D> and FA for each subject were generated on a voxel-by-voxel basis from the sorted eigenvalues of **D** and converted into Analyze (Mayo Foundation, Rochester, MN, USA) format.
Regions-of-interest (ROI) were placed in normal-appearing frontal and occipital white matter and centrum semiovale using the T_2-weighted EP images (See Figure 5.1), Since the T_2-weighted EP images and the DTI parametric maps were by definition co-registered, this allowed <D> and FA values to be measured

simultaneously in the ROI. The observer (TJM) was blind to the clinical status and cognitive function of participants, and purpose of the study.

7.2.3 Statistical analyses

To assess whether WML and DTI parameters followed the expected pattern in this cohort descriptive statistics for WML and DTI for those with and without a self-reported history of CVD are presented. WML rating scale is a short ordered scale (0 to 3) with a positively skewed distribution and therefore non-parametric statistics are used, whereas parametric statistics are used for DTI parameters. X^2 linear by linear association (test for trend) was used to test for a difference between the two groups for WML, and t-test for DTI parameters. Spearman's ρ was used to correlate WML (both DWMH and PVH) with birth parameters, and Pearson's r for DTI parameters (<D> and FA). The role of potential confounders in the relationship between birth and DTI parameters was assessed using partial correlation.

7.2.4 Results

Descriptive statistics: Descriptive statistics for WML ratings for 110 people who underwent brain MRI are presented in Chapter 3 (Table 3.9). For DWMH score 0: n = 8 (7.3%), score 1 n = 78 (70.9%); score 2 n = 17 (15.5%); score 3 n = 7 (6.4%); for PVH score 1 n = 57 (51.8%); score 2 n = 36 (32.7%); score 3 n = 17 (15.5%). The incidental structural findings (meningioma, temporal cyst, pituitary adenoma) did not interfere with coding for WML, and all cases are included in these analyses. Descriptive statistics for <D> and FA are presented in Chapter 3 (Table 3.10). Analyses include 105 subjects (1 excluded due to meningioma, 4 due to technical problems with DTI data). One female has no frontal measures and another no occipital measures due to inability to place a ROI in an area without visible WML.

Table 7.8 shows the WML descriptive statistics for those with and without a history of CVD. There was no statistically significant difference in WML score for those with or without a history of CVD (P >.2), although only 11 (10%) of subjects reported a history of CVD.

Table 7.8 Comparison of WML scores for subjects with or without history of CVD (n=110)

WML score	CVD+ (n=11) n (%)	CVD-(n=99) n (%)	X^2	P
DWMH 0	0	8 (8.1%)		
DWMH 1	7 (63.6%)	71 (71.7%)		
DWMH 2	3 (27.3%)	14 (14.1%)		
DWMH 3	1 (9.1%)	6 (6.1%)	1.7	.20
PVH 1	6 (54.5%)	51 (51.5%)		
PVH 2	3 (27.3%)	33 (33.3%)		
PVH 3	2 (18.2%)	15 (15.2%)	0	1.0

P linear by linear association (df = 1)

CVD+ = history of CVD CVD- = no history of CVD

Table 7.9 shows the DTI descriptive statistics for DTI parameters for those with and without a history of CVD. Subjects with a history of CVD had significantly higher <D> and lower FA in most regions (t-test, **<D>** frontal P = .003, occipital P = .001, centrum semiovale P = .046; **FA** frontal P = .026, occipital .007, centrum semiovale .62).

Table 7.9 Comparison of DTI parameters for subjects with or without history of CVD (n = 105)

	History of CVD Yes (n=10)		No (n=95)		t	df	P
	Mean	SD	Mean	SD			
Frontal <D>	876.9	50.6	835.8	40.3	**3.0**	**102**	**.003***
Occipital <D>	797.2	31.4	757.1	35.2	**3.5**	**102**	**.001***
Centrum semiovale <D>	794.2	45.0	765.4	42.7	**2.0**	**103**	**.046**
Frontal FA	.28	.03	.31	.03	**-2.3**	**102**	**.026**
Occipital FA	.38	.06	.42	.04	**-2.8**	**102**	**.007***
Centrum semiovale FA	.40	.07	.39	.06	.49	103	.62

Bold type: P < .05 * P < .01

The relationship between WML and DTI is described in Table 7.10. Higher scores on WML were associated with higher <D> in frontal (ρ_{PVH} = .31, P = .001; ρ_{DWMH} = .29, P = .003) and centrum semiovale (ρ_{PVH} = .35, P < .001; ρ_{DWMH} = .26, P = .008) regions, but not occipitally (ρ_{PVH} = .10, P = .32; ρ_{DWMH} = .15, P = .13). There were no statistically significant association between WML score and FA in any region (ρ all <.15).

Table 7.10 Relationship between WML and DTI parameters (n = 105)

	Frontal <D>		Occipital<D>		Centrum<D>		Frontal FA		Occipital FA		Centrum FA	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
DWMH 0 n=8	811.7	23.4	756.0	26.4	742.5	23.7	.31	.03	.43	.03	.38	.06
DWMH 1 n=74	837.5	43.1	758.9	36.5	766.6	45.0	.30	.03	.12	.04	.39	.06
DWMH 2 n=15	855.7	41.2	768.7	34.8	782.4	44.0	.31	.03	.42	.04	.42	.06
DWMH 3 n=7	861.4	45.6	772.3	56.0	781.0	32.3	.31	.02	.35	.11	.37	.06
ρ (P)	**.31 (.001)***		.10 (.32)		**.35 (<.001)***		-.05 (.62)		.11 (.25)		.05 (.64)	
PVH 1 n=54	825.9	35.3	757.9	36.3	752.9	34.4	.31	.03	.41	.03	.39	.06
PVH 2 n=34	847.8	36.5	762.2	31.5	783.3	42.6	.30	.03	.43	.04	.39	.06
PVH 3 n=16	869.1	59.7	768.9	48.8	786.6	55.5	.31	.02	.41	.08	.40	.06
ρ (P)	**.29 (.003)***		.15 (.13)		**.26 (.008)***		.05 (.62)		-.01 (.88)		.15 (.13)	

Birth parameters and WML and DTI: Correlations between WML and birth parameters are presented in Table 7.11. All correlations are in a negative direction as hypothesised (ρ 0 to -.29), but only the correlation between placental weight and WML reached conventional statistical significance. As hypothesised, the correlations are stronger for DWMH than PVH (r = -.12 to -.29 for DWMH and r = 0 to -.23 for PVH), although there is no statistically significantly difference between these correlation coefficients.

Table 7.11 Correlations among birth parameters and WML (Spearman's ρ)

	n	DWMH		PVH	
		ρ	P	ρ	P
Hypothesis		negative (--)		negative (-)	
Birth weight	110	-.18	.06	-.09	.32
Birth length	107	-.12	.20	.00	.98
Placental weight	83	**-.29**	**.008**	**-.23**	**.038**
Birth weight corrected for gestational age	100	-.17	.09	-.09	.37

Bold type: P <.05

Correlations among birth parameters and DTI parameters are presented in Table 7.12. The hypothesised associations of a negative correlation between birth or placental weight and <D>, and a positive correlation for FA broadly holds for birth weight in frontal and centrum semiovale region, but does not reach conventional statistical significance. The association is weakened by correcting for gestational age. The pattern for placental weight was more consistent, with all correlations in the expected direction, and three reaching statistical significance (frontal <D> r = -.25, P = .03; frontal FA r = .36, P = .001; centrum semiovale <D> r = -.27, P = .016).

Table 7.12 Correlations among birth parameters and DTI parameters (Pearson's r)

	Frontal <D>		Occipital <D>		Centrum <D>		Frontal FA		Occipital FA		Centrum FA	
	r	P	r	P	r	P	r	P	r	P	r	P
Hypothesis	negative		negative		negative		positive		positive		positive	
Birth weight	-.08	.44	.12	.22	-.12	.23	**.20**	**.04**	-.00	.98	.04	.67
Birth length	.00	.98	.10	.31	-.01	.92	.17	.08	-.09	.34	.08	.42
Placental weight	**-.25**	**.03**	-.05	.65	**-.27**	**.02**	**.36***	**.001**	.004	.97	.05	.67
Birth weight corr for gest age	-.11	.31	.10	.31	-.13	.19	.16	.11	-.01	.96	.04	.70

Bold type: P <.05 * P < .01

The role of potential confounders (age, sex, WML load, prior ability (NART)) was assessed using partial correlation. If correcting for just age and sex, associations were attenuated slightly, but remained statistically significant for placental weight and frontal <D> (r = -.25, P = .029), centrum <D> (r = -.27, P = .017) and frontal FA (r = .38, P = .001). If corrected for all potential confounders (age, sex, WML load, prior ability (NART)) associations with <D> were further attenuated, with placental weight and centrum <D> (r = -.22, P = .05) reaching conventional statistical significance. The effect size for placental weight and frontal FA remained essentially unchanged (r = .40, P < .001).

7.2.5 Discussion

In this study of early life influences on MRI features of CVD there was a trend towards a negative association between birth parameters and WML load. However, only the correlation between placental weight and WML reached conventional statistical significance. The correlations were slightly stronger for DWMH than PVH. For DTI parameters, the hypothesised associations of a negative correlation between birth or placental weight and <D>, and a positive correlation for FA, broadly held for birth weight in frontal and centrum semiovale region, but did not reach conventional statistical significance. The association was weakened by correcting for gestational age. There was a more consistent association between placental weight DTI parameters. The association was attenuated after correction for potential confounders including WML, but remained statistically significant between placental weight and centrum <D> and frontal FA.

This is the first study to investigate early life influences on cerebrovascular disease using MRI (no prior published studies were identified on literature review). Large epidemiological studies have shown an association between birth weight and stroke incidence and mortality (Hypponen et al., 2001; Rich-Edwards et al., 2005), but there is debate as to the importance of stroke sub-type (Rich-Edwards et al., 2005). We used MRI changes as a more specific measure of cerebrovascular (occlusive) disease. Our finding of an association between early life influences and WML, possibly stronger for DWMH than PVH, is consistent with literature suggesting a more

vascular aetiology for DWMH (Schmidt et al., 1993; Schmidt et al., 2004) than PVH (Leaper et al., 2001; Schmidt et al., 2004). WML are crude measures of vascular damage, with multi-factorial aetiology. DTI has been suggested as a more sensitive measure of white matter tract integrity and damage (Basser et al., 1996; O'Sullivan et al., 2001a). The associations of birth parameters with <D> and FA mostly in the expected direction mean that sensitive measures of water diffusion in the brain as a means of determining white matter tract integrity should continue to be explored. As DTI is a non-invasive technique which was well-tolerated even in this elderly cohort it has huge potential as a clinical and research tool (Herneth, 2003; Moseley et al., 2002). However, there is no gold standard for image acquisition or analysis, leading to difficulty in comparing studies. Methodological issues relating to DTI are discussed in detail in Chapters 1.1.3 and 5.4.

<D> increases and FA decreases with age (Nusbaum et al., 2001; O'Sullivan et al., 2001a; Abe et al., 2002), and the incidence of CVD increases with age (Longstreth, Jr. et al., 1996). The relationship between placental weight and <D> and FA may therefore have been confounded by age, even within the narrow age group of this cohort. However, partial correlation correcting for sex and age did not eliminate the relationship. This relationship between birth parameters and DTI may still be due to confounding by other unmeasured factors, and as the exact aetiology of <D> and FA changes are not fully understood (Le Bihan, 2003) this may not necessarily relate to CVD.

The finding of an association between placental weight and both WML and DTI parameters (particularly in the frontal region) adds to the finding of an association between placental weight and self-report of CVD (see discussion above Chapter 7.1.5). The importance of placental size in the development of white matter tracts and their damage over time could be addressed by prospective studies using non-invasive studies which do not involve ionising radiation (e.g. DTI) from a young age.

All associations found here are small to moderate, and the lack of statistically significant associations may be due to lack of power. In the absence of previous

studies of birth parameters and MRI changes we could not accurately estimate a required sample size, but it would be reasonable to assume that more sensitive measures required smaller numbers than epidemiological studies. DTI is an example of a technique which can be used in humans in vivo to gain more direct biological markers of white matter tract damage which will enable mechanistic studies of the determinants of CVD and associated cognitive decline.

7.3 Social class and cerebrovascular disease

7.3.1 Introduction

Studies of early life influences on cerebrovascular disease must consider social class in addition to birth parameters. Social class, birth parameters and later life outcomes such as CVD are often intercorrelated (Osler et al., 2003; Bartley, Power, Blane, Smith, & Shipley, 1994), and it can be difficult to distinguish whether an influence is causally related to the outcome of interest or a confounder of a separate relationship (see Chapter 4.2.4). Social class is related to cardiovascular outcomes, and adverse circumstances in early life have related to stroke risk, possibly more strongly than coronary heart disease (Smith et al., 1998; Hart, Hole, & Smith, 2000), but not in all studies (Eriksson et al., 2000). Some studies have suggested that indicators of poor socioeconomic environment in early life (low birth weight, large family size, low social class) may have stronger links with haemorrhagic than ischaemic stroke (Hart & Smith, 2003).

Using more sensitive indicators of white matter damage, studies have found a relationship with socioeconomic circumstances. Severity of WML increased with decreasing income (Longstreth, Jr. et al., 1996), but few studies of WML include measures of socioeconomic environment. Those that do may include some aspects of the social or economic environment, for example the Rotterdam study includes income, the ARIC study education, and both include smoking history, but neither report occupation of the participant. Inclusion of details from early life social environment, such as parental occupation, is rare. No studies were found which reported the association between DTI parameter changes suggestive of white matter damage (increased <D> and decreased FA) and socioeconomic status.

Therefore, the relationship between social class in childhood and cerebrovascular disease in the Simpson's cohort was investigated at three levels 1) self report of history of stroke or TIA 2) WML on MRI 3) DTI parameters related to white matter tract damage. The hypotheses were that there would be no relationship between social class and self report of stroke disease (due to small numbers and combination of haemorrhagic and ischaemic stroke). Further, we hypothesised that social class would be positively associated with WML (increased deprivation correlating with increased WML load) and <D>, but inversely associated with FA.

7.3.2 Methods

The methods for recruitment, neuropsychological testing and archive data retrieval, including coding of social class, are described in Chapter 2 and 6.2. Imaging methodology is described in Appendix 9.6 and 9.7 and Chapter 5.2 above.

7.3.3 Statistical analyses

Social class was coded using the Registrar General's classification, and class I & II were combined due to small numbers (see Chapter 6.2). All analyses use non-parametric statistics. Descriptive statistics of stroke incidence, WML score and <D> and FA are presented for each social class. The relationship between social class and stroke incidence was investigated using Chi-squared (X^2), and correlations between social class and WML or DTI parameters used Spearman's ρ.

7.3.4 Results

There was no statistically significant difference in parental social class between those with or without a history of CVD ($X^2 = .46$, $P = .50$), but only 11 subjects reported a history of CVD (Table 7.13).

There was no association between WML load and social class for PVH or DWMH (linear by linear association $X^2 > 1.4$, $P = > .1$) (Table 7.14).

Table 7.13: Frequency of history of stroke disease by social class of father at birth (n = 110)

Social class	CVD + n (%)	CVD - n (%)
I & II	0	11 (11.1%)
IIIN	3 (27.3%)	13 (13.1%)
IIIM	4 (36.4%)	41 (41.4%)
IV	1 (9.1%)	15 (15.2%)
V	1 (9.1%)	11 (11.1%)
Illeg	2 (18.2%)	8 (8.1%)
$\mathbf{X^2}$	.46	P = .50

X^2 = linear by linear association (df = 1)
CVD+ = history of CVD CVD- = no history of CVD

Table 7.15 and Figure 7.1 show parental social class by DTI parameters. There is a suggestion of a decrease in <D> with increasing social class, and no clear relationship with FA. Those births classed as illegitimate do not seem to fall as a social class 'below' V, therefore correlations below are presented with illegitimate births excluded (Table 7.16).

Table 7.14: Frequency of WML load by social class of father at birth (n = 110)

Social class	PVH 1 n (%)	PVH 2 n (%)	PVH 3 n (%)	DWMH 0 n (%)	DWMH 1 n (%)	DWMH 2 n (%)	DWMH 3 n (%)
I & II	8 (14.0%)	2 (5.6%)	1 (5.9%)	2 (25.0%)	9 (11.6%)	0	0
IIIN	7 (12.3%)	5 (13.9%)	4 (23.5%)	1 (12.5%)	12 (15.4%)	2 (11.8%)	1 (14.3%)
IIIM	27 (47.4%)	11 (30.6%)	7 (41.2%)	3 (37.5%)	29 (37.2%)	9 (52.9%)	4 (57.1%)
IV	8 (14.0%)	7 (19.4%)	1 (5.9%)	1 (12.5%)	12 (15.4%)	2 (11.8%)	1 (14.3%)
V	5 (8.8%)	6 (16.7%)	1 (5.9%)	1 (12.5%)	9 (11.6%)	2 (11.8%)	0
Illeg	2 (3.5%)	5 (13.9%)	3 (17.6%)	0	7 (9.0%)	2 (11.8%)	1 (14.3%)
X^2	2.7	P = .10		1.4	P = .23		

X^2 = linear by linear association (df = 1)

Table 7.15: Mean and SD of DTI parameters <D> and FA social class of father at birth (n = 105)

Social class (n)	Frontal <D>		Occipital <D>		Centrum <D>		Frontal FA		Occipital FA		Centrum FA	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
I & II (11)	839.9	36.9	766.5	22.0	769.4	31.8	.30	.02	.41	.03	.38	.06
IIIN (16)	864.3	50.2	780.3	30.7	786.1	43.5	.30	.03	.41	.05	.40	.07
IIIM (45)	835.4	34.3	755.5	41.1	762.5	39.7	.31	.03	.42	.04	.40	.05
IV (16)	828.9	36.8	753.0	29.7	756.5	44.6	.31	.03	.43	.05	.38	.07
V (12)	803.3	26.3	753.5	27.4	751.7	27.8	.30	.02	.43	.03	.41	.07
Illeg (10)	867.8	59.8	765.2	48.8	796.5	64.9	.30	.03	.39	.07	.39	.07

Figure 7.1: Mean and 95% confidence intervals of DTI parameters for paternal social class at birth
A) Frontal <D> B) Occipital <D> C) Centrum semiovale <D> D) Frontal FA E) Occipital FA E) Centrum semiovale FA

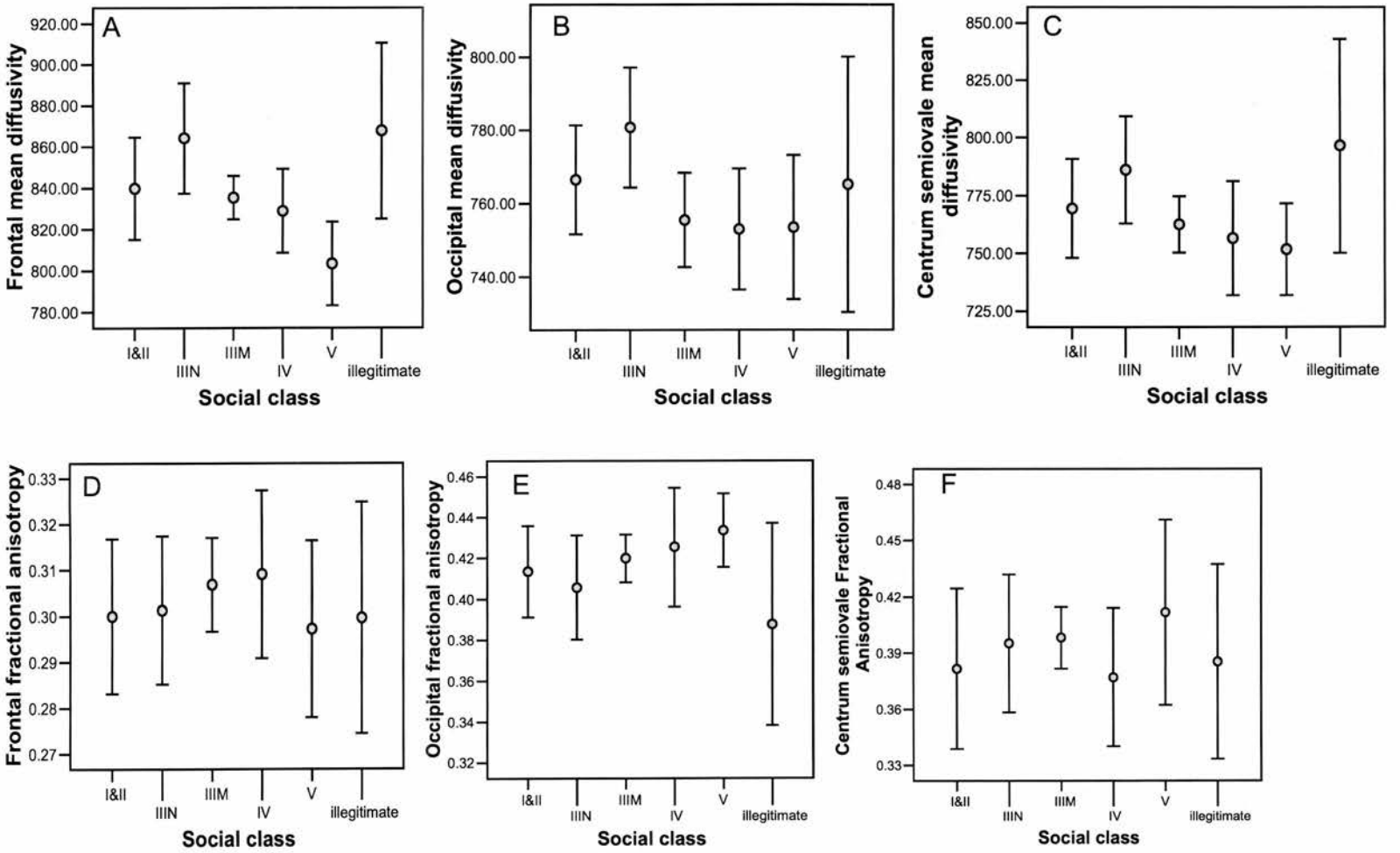


Table 7.16: Correlations between social class of father at birth and WML (n = 110) (Spearman's ρ)

	PVH		DWMH	
	ρ	P	ρ	P
Hypothesis	positive		positive	
Social class (illeg [n=10] excluded)	.05	.64	.08	.42

Table 7.17: Correlations between social class of father at birth and DTI parameters (<D> and FA (n = 105) (Spearman's ρ)

	Frontal <D>		Occipital <D>		Centrum <D>		Frontal FA		Occipital FA	P	Centrum FA	P
	ρ	P	ρ	P	ρ	P	ρ	P	ρ		ρ	
Hypothesis	positive		positive		positive		negative		negative		negative	
Social class (illeg [n=10] excluded)	**-.29**	**.004***	**-.22**	**.03**	**-.23**	**.03**	.05	.65	.18	.08	.01	.89

Bold type: P <.05 * P <.01

Correlations between social class and WML show no significant association) (ρ -.04 for PVH and -.08 for DWMH) (Table 7.16).

For DTI parameters the hypothesis was that increasing social class (deprivation) would be associated with increased <D> (i.e. more diffusivity or 'leaky' white matter tracts) and decreased FA. With births coded as illegitimate are excluded there is a consistent *negative* association between <D> and social class (ρ -.23 to -.29, P <.03) (Table 7.17), i.e. increased deprivation was associated with *less* diffusivity. The association with FA is less consistent, with a non-significant trend towards a *positive* association.

In view of the significant association between social class and <D> in all three regions (frontal, occipital and centrum semiovale), and the association between frontal and centrum semiovale <D> and placental weight (Chapter 7.2.4), a multiple regression model was constructed to predict frontal <D>, with independent variables social class, birth weight and placental weight, age and sex (Table 7.18).

Using stepwise regression, the significant predictors of frontal <D> were placental weight, with <D> decreasing by 78 x 10^{-3} mm^2/s (95% CI 14 to 140) for every kilogramme increase in placental weight, and female sex decreasing <D> by 23.2 x 10^{-3} mm^2/s (95% CI 3.1 to 43.4). Placental weight accounted for 6.1% of the variance in frontal <D> and sex for 6.2% of the variance. With placental weight in the model, social class did not contribute significantly.

Table 7.18: Stepwise multiple regression analysis of frontal <D> on birth weight, placental weight (g), social class, age and sex (n = 77)

	b	SE	beta	t	P	95% CI for *b*	
						Lower	Upper
Constant	908.8	23.8		38.2	.000	843.7	934.6
Placental weight	-.078	.032	-.26	-2.4	.018	-.14	-.014
Sex (female)	-23.2	10.1	-.25	-2.3	.024	-43.4	-3.1

R	R^2	Adj R^2	SEE	F	df regression	df residual	P
0.35	.122	0.099	40.7	5.3	1	75	.024

Residual SD = 39.3

For occipital <D>, the model predicted 14.5% of the variance, with significant predictors age in years (b = 8.6 (95% CI 3.3 to 13.9), R^2 = .121) and social class IIIN (class V as reference) (b = 22.2, 95% CI .49 to 44.0, R^2 = .046).
For centrum semiovale <D>, the model predicted 11.5% of the variance, with significant predictors age in years (b = 7.4 (95% CI 1.2 to 13.7), R^2 = .085) and placental weight (b = -.072, 95% CI -.136 to -.007, R^2 = .056).

7.3.5 Discussion

As hypothesised, there was no significant relationship between social class and self report of stroke disease. Contrary to the hypothesis of a positive association of social class and WML there was no significant association between WML load and social class for PVH or DWMH. For DTI parameters the hypothesis was that increasing social class (deprivation) would be associated with increased <D> and decreased FA. However, there was no significant association for the whole cohort, and after excluding illegitimate births there was a *negative* association between <D> and social class. The association with FA was less consistent. Stepwise multiple regression suggested that social class did not significantly predict <D> if placental weight, age and sex were added to the model. The models explained only 10-15% of the variance in <D>, leaving a substantial proportion to be accounted for by other variables.

The lack of an association between social class and self report of stroke is likely to be due to the small numbers of subjects in this study reporting a history of stroke, misclassification bias due to self-report, and the inability to distinguish ischaemic from haemorrhagic stroke (see Chapter 7.1.5).
The lack of association between social class and WML may similarly have been due to lack of power, or be a consequence of the non-specific and multifactorial nature of WML. Cluster analysis from the Cardiovascular Health Study (n = 3,230) has suggested that infarcts and leukoaraiosis have different aetiologies (Longstreth, Jr. et al., 2001).

This study was novel in investigating the association between social class and DTI parameters. Previous studies have shown an association between poor socioeconomic

environment or low income and increased morbidity and mortality from stroke (Eriksson et al., 2000) (especially haemorrhagic) (Hart et al., 2003). Chronic cerebrovascular disease is associated with relatively high <D> is and low FA (Sotak, 2002; LeBihan et al., 2001), therefore the hypothesis was that poor socioeconomic environment (high social class) would be associated with high <D> and low FA. The negative association between <D> and social class was therefore unexpected, and may have been due to chance. Measures of <D> are much more reproducible and consistent across the brain than FA, which is exquisitely sensitive to the position of the regions of interest (Pfefferbaum et al., 2003). The biological basis of DTI changes continues to be investigated (Le Bihan, 2003) and studies of the difference between haemorrhagic and ischaemic stroke could be productive. Diffusion weighted MRI studies have suggested that DWI imaging can differentiate aetiologies of stroke (e.g. cardioembolic from large artery atherosclerosis) (Bonati, Lyrer, Wetzel, Steck, & Engelter, 2005). Future DTI studies should include demographic data on socioeconomic variables.

Entering both social class and placental weight (and age and sex) into a multiple regression found that social class was no longer a significant predictor of <D> in frontal and centrum semiovale regions of interest. Social class could therefore be a confounder in this relationship, or it could be causally linked to both white matter tract damage and placental weight. Future studies are required to investigate the relative importance of these early life influences.

It should be noted that data on placental weight was only available on a proportion of subjects (83/110 = 75.5%), and therefore whenever this variable was included in the model there is a substantial loss of information from other variables. The placenta should be considered as an important conduit of oxygen and nutrients to the developing fetus, and included where possible in studies of early life determinants of cerebrovascular disease.

7.4 Apolipoprotein E

7.4.1 Introduction

The Apolipoprotein E gene *(APOE)* has been associated with age related cognitive impairment as well as Alzheimer's disease (see Chapter 6.3.1). Because *APOE* alters circulating levels of cholesterol, its association with cardiovascular disease has been examined. *APOE* is the gene most strongly related to normal cholesterol variability, and has been reported as accounting for around 6% of the variation in risk for coronary heart disease (Eichner et al., 2002). However, the evidence to date for other cardiovascular diseases and their risk factors (thrombotic stroke, hypertension, peripheral vascular disease) suggests that *APOE* "is not considered a major risk factor for these vascular disorders" (Eichner et al., 2002) (p. 490).

The Rotterdam study (n = 6,852) did not find an association between *APOE* and stroke incidence (Slooter et al., 2004). In a subgroup of 971 subjects there was a significant association between *APOE*e4 and subcortical but not periventricular WML (de Leeuw et al., 2004), particularly for those with hypertension. In the Cardiovascular Health Study (n = 3,469) there was no relationship between presence of *APOE*e4 and presence of infarcts or WML on MRI (Kuller et al., 1998). No studies were found of the relationship between *APOE* and DTI parameters.

Several studies have examined the relationship between *APOE* and markers of atherosclerosis. For carotid atherosclerosis there is equivocal evidence (Manolio, Boerwinkle, O'Donnell, & Wilson, 2004). In the Framingham offspring study (n = 2,723) *APOE*e2 was associated with lower carotid IMT (0.67 vs. 0.73 mm) and stenosis >25% (odds ratio = 0.49; 95% confidence interval = 0.30-0.81) for women. For men *APOE* genotype was not associated with carotid IMT or stenosis in the whole group; however, among men with diabetes, *APOE*e4 carriers had a higher internal carotid artery IMT (1.22 mm) than the *APOE*e3 carriers (0.90 mm) or the *APOE*e2 carriers (0.84 mm) (Elosua et al., 2004). In the Perth Carotid Ultrasound Disease Assessment Study (n = 1,109) (Beilby et al., 2003) there was an association between *APOE*e4 and plaque for men only (odds ratio for each *APOE*e4 allele 1.72 (95% CI 1.05 to 2.80)), and no association between *APOE* and IMT (Souza et al.,

2003). A study of 226 patients with coronary artery disease in Spain did not find an association between IMT and *APOE* (Fernandez-Miranda et al., 2004). Few studies have studied the relationship between *APOE* and peripheral vascular disease. The Honolulu Asia ageing study (n=3,161) found no association between peripheral arterial disease (ABPI <.9) and *APOE* in current or ex-smokers, but a suggestion of an interaction between *APOE* status and diabetes in non-smokers (Resnick et al., 2000).

In the Simpson's study the relationship between *APOE* genotype and (1) markers of atheroma (carotid stenosis or IMT, ABPI) (2) brain imaging markers of cerebrovascular disease (WML and DTI parameters <D> and FA) was investigated.

7.4.2 Methods

The methodology of recruitment and testing is described in Chapter 2. Methodology for collection of ABPI and CIMT is presented in Chapter 2.6 and Appendix 9.5; for imaging Chapter 2.8 and Appendix 9.6 and 9.7; and for genotyping in Chapter 2.6.1 and Appendix 9.4.

7.4.3 Statistical analyses

Frequencies of *APOE* alleles are shown in Table 3.6 (e2 = 8.8%, e3 = 69.6%, e4 = 16.2%). No subjects possessed two *APOE*e4 alleles, 34 (30.9%) were e4+ and 71 (64.5%) were e4-. The sample is in Hardy Weinberg equilibrium ($X^2 = 3.92$, df = 2, P>.1) (Christensen, 2005). For those with and without the *APOE*e4 allele mean (SD) of CIMT and ABPI, and <D> and FA are presented. Statistical significance for the difference between carrier and non carrier was tested using t-test (equal variance assumed as Levene's test P>.5). For carriers and non-carriers the proportion with each degree of carotid stenosis and WML is presented, and tested for statistical significance using X^2 (linear by linear association) test for trend.

7.4.4 Results

There was no statistically significant difference between carriers of the *APOE*e4 allele and non-carriers in IMT (mean difference .03 t = .83, P .41) or ABPI (mean

difference .01, t = .38, P .70) (Table 7.19), or proportion of carotid artery stenosis (X^2 =.06, P .81) (Table 7.20).

Table 7.19: ABPI and carotid IMT for carriers and non-carriers of *APOE*e4

	e4+			e4-			Mean			
	n	Mean	SD	n	Mean	SD	diff	t	df	P
ABPI	34	.93	.18	70	.89	.20	.03	.83	102	.41
IMT	34	.94	.20	71	.92	.18	.01	.38	103	.70

Table 7.20: Proportion of maximal carotid artery stenosis for carriers and non-carriers of *APOE*e4allele (n=105)

% stenosis	e4+		e4-				
	n	%	n	%	X^2	df	P
0-20	19	55.9	41	57.7			
21-40	11	32.4	16	22.5			
41-60	1	2.9	6	8.5			
61-80	1	2.9	6	8.5			
>80	2	5.9	2	2.8			
Total	34		71		.06	1	.81

There were no statistically significant differences between carriers of the *APOE*e4 allele and non-carriers in WML load (DWMH X^2 =3.7, P .30; PVH X^2 = 2.8, P .25) (Table 7.21) or any DTI parameter (Table 7.22).

Table 7.21: Proportion of WML for carriers and non-carriers of *APOE*e4 allele (n=105)

WML	e4+ n	%	e4- n	%	X^2	df	P
DWMH 0	1	2.9	7	9.9			
DWMH 1	25	73.5	50	70.4			
DWMH 2	4	11.8	11	15.5			
DWMH 3	4	11.8	3	4.2	3.7	3	.30
PVH 1	15	44.1	39	54.9			
PVH 2	11	32.4	24	33.8			
PVH 3	8	23.5	8	11.3	2.8	2	.25

Table 7.22: Mean (SD) DT-MRI parameters for carriers and non-carriers of *APOE*e4 allele (n = 100)

	e4+ n	Mean	SD	e4- n	Mean	SD	t	df	P
Frontal <D>	33	845.7	44.4	66	837.9	42.8	.84	97	.40
Occipital <D>	32	758.5	37.9	67	761.7	36.3	-.40	97	.67
Centrum <D>	33	771.5	51.4	67	766.5	37.7	.56	98	.98
Frontal FA	33	.31	.03	66	.30	.03	1.16	97	.25
Occipital FA	32	.43	.04	67	.41	.05	1.41	97	.16
Centrum FA	33	.39	.05	67	.39	.06	-.23	98	.81

7.4.5 Discussion

In this cohort of relatively healthy, community dwelling volunteers aged 75-81 years there was no statistically significant association between *APOE*e4 carrier status and markers of atheroma (carotid stenosis, IMT, ABPI), brain WML or DTI parameters.

Although this study is relatively small, and therefore lacks power to test these hypotheses, the results concur with previous studies which did not find an association between *APOE*e4 and carotid atheroma (Souza et al., 2003; Fernandez-Miranda et al., 2004), ABPI (Resnick et al., 2000), or WML (Kuller et al., 1998). Those studies which have found a statistically significant association between *APOE* genotype and

carotid stenosis (Elosua et al., 2004) or IMT (Beilby et al., 2003; Elosua et al., 2004), have had subject numbers over 1,000, and found these associations in subgroup analyses. The current study lacked power to test the relative importance of *APOE* status and various vascular risk factors such as smoking (Resnick et al., 2003), hypertension (de Leeuw} and diabetes, which have been found to interact with *APOE* status in previous studies (Elosua et al., 2004). The small numbers of subjects in the current study and the multiple outcomes considered mean that the results should be treated cautiously. No previous studies were identified relating DTI parameters to *APOE* status.

The finding of an association between *APOE*e4 and cognitive ability in older age (see Chapter 6.3) but not markers of cerebrovascular disease, suggests that the genetic influence of *APOE* results in pathological changes that may be distinct from cerebrovascular disease, and more related to Alzheimer's type pathology (Farrer et al., 1997). However, cardiovascular disease is a complex clinical outcome, encompassing coronary heart disease, CVD (stroke, TIA), peripheral arterial disease etc. (Eichner et al., 2002), and there is strong evidence for a relationship between *APOE* and some cardiovascular risk factors (e.g. hypercholesterolemia) and outcomes (Eichner et al., 2002). Future genetic studies need to be more specific in recording outcomes of large versus small vessel disease, ischaemic versus haemorrhagic stroke, and should acknowledge that (poly)genetic mechanisms may affect both the aetiology of and recovery from these diseases (Markus, 2003). Sample sizes of over 1,000 subjects would be required. Non-invasive, sensitive, brain imaging techniques (e.g. DTI) which can be performed longitudinally are promising for future study.

In this chapter early life influences - covering genetics, early life biology and social environment - on cerebrovascular disease were investigated. Cerebrovascular disease was examined using a novel, relevant basket of phenotypes related to CVD: a dichotomous outcome by subject self report, presence of WML and DTI parameters on neuroimaging, and markers of atheromatous load (carotid stenosis and IMT). There was a small increase in self-report of cerebrovascular disease with increasing

placental weight, and a weak negative correlation between birth parameters, particularly placental weight, and both WML load, and decreasing <D> and increasing FA. There was no significant relationship between birth parameters and markers of atheroma. Social class was not significantly associated with stroke self-report or WML. There was an unexpected association between increasing deprivation and decreasing <D>, but social class did not contribute to <D> independently of placental weight. *APOE*e4 carrier status did not relate to markers of atheroma, WML or DTI parameters.

The multiple comparisons between early life variables and CVD outcome measures are a major weakness in this study, particularly in view of the relatively small number of subjects (and especially when considering the subject's own self report of CVD as an outcome measure which is prone to bias). Chapter 8 will discuss the main results and methodological limitations in more detail.

8 Discussion

8.1 Main results

In this thesis life course influences on cognitive ageing and associated cerebrovascular disease were investigated in a well-characterised cohort of community-dwelling people aged 75-81 who had been born in Edinburgh hospitals between 1921 and 1926. The aims of the thesis were to investigate (1) the relationship between brain structure (volume, WML and DTI parameters) and cognitive ability, (2) the relationships among birth parameters (weight, length, placental size), social class, the *APOE* gene and cognitive ability, and (3) the relationships among birth parameters, social class, the *APOE* gene and cerebrovascular disease (using markers of vascular risk i.e. carotid artery stenosis and IMT, and ABPI).

The main results were firstly, for brain structure and cognitive ability: (a) a small to moderate positive association between the general cognitive factor (*g*) and both whole brain volume and intracranial area; (b) a non-statistically significant trend towards a negative association between WML and fluid but not crystallised cognitive ability; (c) a pattern of increasing <D> and decreasing FA associated with decreasing cognitive ability, statistically significant for frontal <D> and verbal fluency. Secondly, for birth parameters and cognitive ability: (a) a small positive association between birth weight and cognitive ability (Raven's matrices) in old age, partly but not fully explained by this association in earlier life; (b) a weak relationship between social class and cognitive ability in childhood but not later life; (c) possession of the *APOE*e4 allele was associated with worse performance on the logical memory test only. Thirdly, for birth parameters and cerebrovascular disease (a) a small increase in self-report of cerebrovascular disease with increasing placental weight; (b) a weak negative correlation between birth parameters, particularly placental weight, and both WML load and DTI parameters; no significant relationship between birth parameters and markers of atheroma (c) no significant association between social class and stroke self-report or WML; an inverse relationship between social class and <D>, but social class did not contribute to <D> independently of placental weight; (d) no

significant association between *APOE* *4 carrier status and markers of atheroma, WML or DTI parameters.

Detailed discussion of each of these results is presented in the relevant chapters. This general discussion considers firstly the main results, highlighting where these add to the current literature; secondly the methodological limitations of the study; thirdly potential mechanisms to explain the results and finally some suggestions for future research.

For brain structure and cognitive ability this study adds to the literature (McDaniel et al., 2002) which shows an association between adult cognitive ability and structural brain parameters. In particular it confirms a prior study that found that this is largely due to the persistence of this association from earlier life (MacLullich et al., 2002). This study is the first to find this in such an elderly group of predominantly women, with a narrow age range. The accumulation of WML had a weak negative association with fluid intelligence, only reaching conventional statistical significance for MMSE, but no association with crystallised intelligence. WML may be one determinant of cognitive decline (Gunning-Dixon et al., 2000), but WML seen on structural MRI scans are relatively non-specific, and seen in a variety of clinical situations (e.g. multiple sclerosis, stroke disease) (Vermeer et al., 2003b). DTI parameters were found to be a sensitive measure of ultrastructural brain damage that related to cognitive impairment, particularly for verbal fluency (Shenkin et al., 2003; Shenkin et al., 2005). DTI therefore has promise in investigating the biological mechanisms of cognitive decline (Le Bihan, 2003; O'Sullivan et al., 2001a). Studies of cognitive ageing should include measures or estimates of early life ability. As few studies will have access to records of actual ability in earlier life, tests of crystallised ability such as the NART should be used. Studies of cognitive ageing should also include a general cognitive factor (*g*) derived as a latent trait from the tests of specific abilities used as this will allow comparison between studies using different test batteries. Neuroimaging studies should consider current and prior brain volume as well as the burden of WML.

Studies of birth parameters and cognitive ability have mostly included children (Bhutta et al., 2002) or young adults (Sorensen et al., 1997; Richards, Shipley, Fuhrer, & Wadsworth, 2004; Seidman et al., 1992). Only two studies have included older people (aged around 70) (Martyn et al., 1996; Gale et al., 2003) and did not find a significant relationship. It has been suggested that any relationship in older age is largely explained by the correlation between birth weight and childhood ability (Richards et al., 2002). In the Simpson's study we did find a relationship between birth weight and cognitive ability almost eight decades later, which was only partly explained by earlier ability. This positive result may be due to chance and requires to be replicated in other studies, but the potential for very early interventions to affect cognitive ability eight decades later has important public health implications, given the increasing prevalence of cognitive decline and its social impact (Scottish Executive, 2002). However, the effect size is small, and genetic and later life environmental factors have a more substantial influence on cognitive ability than birth weight (Shenkin et al., 2004). The finding that social class influences cognitive ability in childhood but not adulthood is consistent with previous studies showing that the influence of the shared environment decreases with time (Bouchard, Jr., 1998), and underlines the importance of a life course perspective (Kuh et al., 2003). Studies including socioeconomic variables need to collect data from different times in the life course (Bouchard, Jr., 1998). Genetic influences should also be considered (Plomin, 1999), but any influence on intelligence is likely to be due to multiple genes (Deary, 2004). Of the genes identified to date *APOE* has the most common variants and therefore this study, with n of 110, could investigate the importance of *APOE* status on cognition and cerebrovascular disease. *APOE* was found to be related to logical memory but not general cognitive ability or cerebrovascular disease, suggesting that it may be specific to memory (Small et al., 2004), perhaps due to Alzheimer's type pathology (Farrer et al., 1997).

Previous epidemiological studies of birth parameters and cerebrovascular disease have found an association between birth weight and stroke morbidity and mortality (Rich-Edwards et al., 2005; Hypponen et al., 2001). The association of placental weight and various measures of CVD suggests that placental integrity may be

important in the development of CVD (Jackson, 1996). A functioning placenta is required for adequate transfer of oxygen, nutrients and hormones (insulin and IGF) to the developing fetus, and placental weight is a crude estimate of function (Sibley et al., 2002; Hargitai et al., 2004). Maternal nutrition will influence fetal nutrition, but birth weight is only affected under conditions of extreme compromise (Stein, Susser, Saenger, & Marolla, 1975; Stein, Zybert, van de, & Lumey, 2004), although nutrient status at conception and nutrient balance may be more important than absolute intake (Gluckman et al., 2005). Maternal physiology and utero-placental function are also major factors in nutrient transfer. Studies of prenatal influences on CVD should, where possible, include assessment of placental function. The lack of a relationship between social class at birth and CVD was surprising, and may have been due to specific characteristics of the social circumstances of this cohort. Alternatively, the method of defining social class may have been important (Craig & Forbes, 2005), or possibly a lack of power, when using categorical data with relatively little variance. The finding of an association between increasing deprivation and decreasing <D> rather than increasing <D> as hypothesised was unexpected and again may have been due to chance or the method of classifying social class (using father's occupation at birth only): socioeconomic influences on CVD may be stronger at different periods in the life course. *APOE* does not appear to be a significant risk factor for CVD (Souza et al., 2003).

8.2 Methodological limitations

This study has several methodological limitations which limit the conclusions which can be drawn from the results, and the degree to which they can be applied to other samples and populations. The initial study design was a historical cohort study tracing survivors of hospital births in 1921 who sat the Moray House Test in 1932, thus collecting not only birth data but also cognitive ability data at age 11. However, loss to follow-up meant that insufficient numbers were recruited (see Chapter 2), and data protection concerns then meant that subsequent subjects were volunteers born in 1922 – 26 who did not sit the Moray House Test, and who were recruited by public appeal. Therefore, the final design is essentially a cross-sectional study of older people with some retrospective collection of data from 75-81 years previously (Abramson & Abramson, 1999), and the ability to validate an estimate of childhood

cognitive ability (Deary et al., 2000). Cross-sectional studies in cognitive ageing are common, but generally they compare young and old people and suggest that differences are due to age (Ebrahim, 1996), whereas they may be due to other effects such as differences in the environment during development: 'cohort effects' (Hennekens et al., 1987). The Simpson's study aimed to study people with a very narrow age range to minimise the effect of age, but still found an association between age and DTI parameters (Shenkin et al., 2005). Therefore, in older people it is important to consider their exact age, and recognise that there may be substantial differences between individuals just a few years apart in age.

Issues which limit the internal validity of a cohort study are bias, chance and confounding (Hennekens et al., 1987). Bias is any systematic error that results in an incorrect estimate of the association between predictor and outcome. The major potential source of bias in cohort studies is loss to follow-up, a particular problem when birth records are used, and individuals recruited 80 years later. The extent of bias can be determined by comparing those who do and do not participate, but only if these data are available. For the 31 births in 1921 we could compare birth characteristics of the participants with the 954 who were not traced, but we could not do this for the 79 subjects born in other years as we only had ethical approval to retrieve birth details of those who gave us permission. The relationship between birth parameters and cognitive ability or cerebrovascular disease would only be biased if the loss to follow-up was related to both the exposure and other risk factors of the outcome under study (Martyn et al., 1996; Joseph & Kramer, 1996). It is also likely that the sample studied may not be typical of older people in Edinburgh, as they were volunteers who responded to a letter or advert. We attempted to maximise generalisability by having no strict exclusion criteria, but volunteers had to deem themselves fit to participate (and having no contraindications to MRI), and their general practitioner had to agree. Without collecting data on the entire eligible population who did not volunteer we cannot determine the full extent of potential bias. The sample had a slightly higher IQ than the general population (estimated by NART as 106), although lower than male subjects specifically selected to be healthy

(MacLullich et al., 2002). Subjects had a similar prevalence of vascular risk factors as other neuroimaging studies of older people (Fotenos et al., 2005).

Another potential source of bias is the use of self-report history of disease and medication use. This could have led to misclassification of people who were not aware of prior diagnoses of stroke, or cardiovascular risk factors (Ebrahim, 1996). In view of the small numbers of people involved in this study, more sensitive outcome measures were used (e.g. DTI parameters), and analyses using self-report data are treated with caution. In the absence of more sensitive markers the subjects' self report could be validated by checking with general practitioner records.

Another potential limitation is the size of the study, and by performing multiple correlations the results may be due to chance. In epidemiological terms it is small: for example, with 110 subjects, to detect statistical significance ($P < .05$) at 90% power a correlation coefficient would need to be larger than .27 (at 80% power >.235) (clara.net, 2005). To demonstrate statistical significance ($P <.05$) with 90% power with a correlation coefficient of .1 (the average effect size of birth weight on cognitive ability (Shenkin et al., 2004)) would require a sample size of 850, (620 for 80% power) (UCLA department of statistics, 2005). This was the rationale for using more sensitive measures of vascular risk (e.g. CIMT or ABPI) than self-report of stroke history, although some have suggested that proxy measures, in particular blood pressure, may in fact have a weaker relationship with early life parameters than actual disease outcomes assessed in large enough populations over a sufficient time interval (Gluckman et al., 2005). Previous epidemiological studies of birth weight and cognitive ability in adulthood that tested participants cognitively rather than relying on retrospective test results have *n*s of 1,576 (Martyn, 1996), 2,136 (Richards et al., 2002) and 4,793 (Gale et al., 2003) but none included participants as old as our study, or such a comprehensive test battery. In terms of neuroimaging, however, this study is, larger than many which include psychometric tests in older people (see (Gunning-Dixon et al., 2000)) (although there are several notable large studies of brain structure and cognitive ability e.g. the Rotterdam study (age 60-90, n 1,077) (de Groot et al., 2000), the Cardiovascular Health Study (age > 65, n = 3,301)

(Longstreth, Jr. et al., 1996) and the ARIC study (age 55-72, n = 1,538) (Mosley, Jr. et al., 2005)). Our study is, however, substantially larger than any previous study of DTI and cognitive ability in old age (e.g. (Madden et al., 2004) n = 16 (O'Sullivan et al., 2001a) n = 17, (Stebbins et al., 2001b) n = 10: see Chapter 5.1).

Confounding – where other variables wholly or partly explain the relationship between the risk factor and outcome - is particularly important in assessing the influence of early life variables on later health and disease studies. Analyses are limited by which confounders are measured and recorded in the original sources. For example, some studies do not have gestational age recorded (e.g. Richards et al., 2004; Rich-Edwards et al., 2005). We relied on the record of the parent's social class as reported to hospital staff, which may have been biased. Other studies have included potential confounders such as parental education or income, but we did not have these data available. Data on placental weight and gestational age were not available for all subjects (Shenkin, 2002). The use of the term confounder is more common in epidemiological than psychological literature, and describes an effect by a factor associated both with the exposure (such as birth weight) and the outcome (cerebrovascular disease or cognitive ability) (Singh-Manoux, 2005). This is partly because it is relatively easy to assess the influence of a potential confounder on binary outcomes. Methodology used more commonly in psychology, such as path analysis and structural equation modelling, can accommodate the concept that a potential confounder may in fact be on the causal pathway (i.e. a mediator) between the independent and dependent variables (Batty et al., 2005). For example, in Developmental Origins research social class is often considered a confounder (Hack et al., 1992) but social class may also be on the causal pathway (Kuh et al., 2004b). The socioeconomic environment can form 'chains of risk' or 'protective chains' that affect disease risk through exposures to causal factors (such as smoking or stress), and thus affect the outcome. Another potential confounder or mediator in the relationship between birth weight and cognitive ability which is seldom included in analyses is maternal ability: in one large nationally representative sample the association between birth weight and childhood IQ was substantially explained by

mother's IQ (Deary, Der, & Shenkin, 2005). This may be due to a variety of reasons such as genetic factors or differing health behaviours in pregnancy.

Epidemiology is the study of distribution and determinants of disease in the population. A sample is studied, and if this sample is selected randomly from the population, then findings in the sample are thought to reflect the general population (Fletcher, Fletcher, & Wagner, 1996; Hennekens et al., 1987), that is, have external validity. Depending on the power of the study these can be generalised with more or less confidence to similar populations. The external validity of a study with n of 110 using data from almost one century ago, and where selection was not random, has to be questioned (Tait, 1974; 1998). Not only were conditions in the 1920s very different from the 2000s, also babies born in Edinburgh hospitals were not typical of births in Edinburgh in the 1920s (Edinburgh Council of Social Service, 1926). Those born in hospital were more likely to be unsupported mothers or those with anticipated or actual complications (Sturrock, 1958; Miller, 1937). This group may therefore have a different relationship between birth parameters and cognitive ability or cerebrovascular disease than the general population. Although this limits the generalisability of the results it is not necessarily a weakness in the design. Some cohort studies intentionally restrict the group studied to those with 'special exposure' (e.g. industrial workers) to increase the chance of determining outcomes following rare exposures (Hennekens et al., 1987). Those born in Edinburgh hospitals could similarly be seen as a high risk group and the relationship with outcomes could be enhanced.

It should be noted that the effect size of many of the correlations in this thesis is small to moderate, with for example, birth weight explaining around 1% of the variance in cognitive ability (Shenkin et al., 2004), placental weight explaining 8% of the variance in WML load and frontal <D> explaining 6% of the variance in verbal fluency. However, even such small influences can have important effects at a population level if they are amenable to intervention (Rose, 1992).

8.3 Potential mechanisms

The study of the Developmental Origins of Health and Disease has moved from descriptive epidemiological studies to using the results of these studies to provide targets for investigating potential mechanisms in humans and animals. The first mechanism to be considered was the role of maternal nutrition in the aetiology of low birth weight (Barker, 1998): Developmental Origins research has focussed on birth weight as a predictor of health and disease in later life, but does not consider birth weight as causal in the pathway to disease, but rather as a proxy measure of the impact of early developmental factors (Gluckman et al., 2005). An association between maternal nutrition and birth weight has been shown in animal models (Langley-Evans, 2004), but the evidence in human studies is less conclusive (Gluckman et al., 2005; Stein et al., 2004). Maternal nutrition is not equivalent to fetal nutrition, and the integrity of the placenta and its transport mechanism must also have an important role (Gagnon, 2003; Sibley et al., 2002; Hargitai et al., 2004). Other potential explanations include deficiencies in specific macro or micronutrients, or excess of potential toxins such as iron or lead.

The consistent association between birth weight and the metabolic syndrome (hypertension, glucose intolerance and raised triglycerides, particularly in the context of obesity) (Barker, 1998) led to the hypothesis of 'brain sparing' (Scherjon, Oosting, Kok, & Zondervan, 1994). This suggests that

"a human baby receiving an inadequate supply of nutrients or oxygen may protect its brain. One way in which it does this is by diverting more blood to the brain at the expense of the blood supply to the trunk. The growth of organs such as the liver is therefore "traded off" to protect growth of the brain" (Barker, 2004) (p 114).

'Brain sparing' has been used to explain the findings of the Dutch Hunger Winter, where babies exposed to famine in the third trimester were retarded in terms of weight, and less so in length or head circumference. There was no association between famine exposure and cognitive performance in adolescence (Stein et al., 1975). The finding of an association between birth weight and cognitive ability in other studies suggests, however, that any protection to the brain is not adequate. Two main environmental hypotheses have been proposed for mechanisms by which low birth weight is associated with adult disease, and in particular brain function. One is

fetal undernutrition as discussed above, and the second is overexposure of the fetus to glucocorticoids (Drake & Seckl, 2004). In addition genetic factors may influence both birth weight and disease risk.

Hormonal influences are implicated in both growth and cognition. Glucocorticoids reduce birth weight and placental size, and are essential for brain development (Drake et al., 2004). Perinatal glucocorticoids or stress programme changes in the hypothalamic-pituitary-adrenal axis (Welberg & Seckl, 2001), and may alter brain structure and function: for example, increased cortisol is associated with poorer cognitive performance in elderly men (MacLullich et al., 2005). Possible common final mechanisms include the Insulin-like Growth Factors (IGF) which play a critical role in determining fetal and placental growth, but also target brain areas responsible for cognition (Berger, 2001). Thyroid hormone also has somatic and cognitive effects, and may interact with IGF (Richards et al., 2002). As cortisol levels influence thyroid hormone and IGF these hormonal influences may interact to affect growth and/or cognitive development (Gluckman et al., 2005). Insulin resistance, which has been related to low birth weight and rapid post-natal growth, is associated with cognitive impairment in the presence of subcortical features, suggesting that insulin resistance might contribute to cognitive impairment through a vascular mechanism (Geroldi et al., 2005).

The molecular basis of programming these functional changes may be epigenetic changes (i.e. changes in the conformation of chromatin without a change in DNA sequence) due to DNA methylation (Reik & Walter, 2001; Young, 2001). The genes most likely to be involved in nutritional programming during early development have not yet been identified. Potential candidates are genes known to determine birth weight or placental development, and research is ongoing to identify whether dietary effects on methyl-group metabolism may affect the oocyte and pre-implantation embryo (Young, Rees, & Sinclair, 2004). Postnatal behaviour in rats has been shown to have reversible epigenetic effects, with nursing behaviour affecting DNA methylation at the glucocorticoid receptor, and altering glucocorticoid receptor

expression in the brain (Weaver et al., 2004). Epigenetic changes have therefore been implicated as a mechanism for programming both before and after birth.

Understanding of mechanism is required before intervention to reduce the impact of disease can be advocated. This study found an association between birth parameters and CVD but not markers of atheroma, which suggests that any influence of birth weight on CVD is not through traditional risk factors causing atheroma. The pathophysiology of cognitive impairment associated with CVD (vascular cognitive impairment, VCI) is still not fully understood (Bowler & Hachinski, 2003). Generalised atherosclerosis, determined by the relatively crude method of history of cardiovascular pathology and ECG changes, has been associated with cognitive decline (Vinkers et al., 2005). The underlying pathology appears to be subcortical ischaemic vascular disease due to stenosis or occlusion of small perforating arteries (DeCarli et al., 2005b; Pantoni et al., 1997), or breakdown of the blood-brain barrier (Wardlaw et al., 2003). There is some overlap in the pathologies underlying CVD and Alzheimer's type dementia (Skoog & Gustafson, 2003). There is no standard treatment for VCI, and little is known about primary or secondary prevention, apart from direct extrapolation from study of stroke as to the importance of treating vascular risk factors (O'Brien et al., 2003). Therefore there is a need for studies of causal and pathological factors over the life course to enable therapeutic advances.

Currently it is felt that there is insufficient evidence for prenatal interventions to influence later disease risk (Joseph et al., 2004). Indeed there may be a risk to health from doing so, as increasing fetal size may increase the need for caesarean deliveries, or maternal obesity and thus adversely affect the health of mother and child. If the 'predictive adaptive response' model (Gluckman et al., 2005) is correct, the fetus is programmed to expect throughout life the level of nutrition it received prenatally, therefore nutritional interventions may require to continue life-long. Attempts to influence postnatal weight may reduce initiatives to increase breastfeeding. It may be that nutritional interventions aimed at chronic disease should be targeted around the period of conception (Young et al., 2004), but the current priority should remain on

improving the health of children born into extreme poverty who have a high risk of low birth weight and prematurity (Boyce et al., 2004).

8.4 Future research

Correlations in observational studies do not necessarily imply causation, but identify potential targets where the search for biological mechanisms may be most fruitful. Here some suggestions are made for future research in the areas investigated in this thesis.

Firstly, in neuroimaging. Neuroimaging studies in cognitive ageing have tended to describe either atrophy or WML, but there is now a move away from this artificial distinction (Drachman, 2005), and a realisation that both atrophy and WML need to be considered as they may have different or cumulative effects (Mosley, Jr. et al., 2005; Kuller et al., 1998). This thesis showed different influences of atrophy and WML on cognition, and would support a shift to considering both outcome measures together. One research group has coined the term "Subclinical Structural Brain Disease" (SSBD) to encompass cortical atrophy, central atrophy, DWMH and PVH (Cook et al., 2002), but this has not been generally accepted. It is important that cognitive ageing studies consider both atrophy and WML, and develop a consensus on the methodology for doing so: brain volume can be measured in several ways (Ferguson et al., 2005) and there are numerous semi-quantitative scales (e.g. (Scheltens et al., 1998; Fazekas et al., 2002) as well as volumetric (Prins et al., 2004) methods of measuring WML. DTI has considerable potential for the study of the structure of white matter structure that underlies cognition and vascular risk (Moseley et al., 2002). Other imaging techniques may be useful, for example Magnetisation Transfer (MT-MRI) which assesses the efficiency of the magnetisation exchange between the protons of water inside tissues and those bound to macromolecules. This may be an important technique to study the role of myelin in cognition (Armstrong et al., 2004). Our neuroimaging data collected on a relatively healthy group of older people can be combined with other data sets for novel purposes: for example it has been combined with another study to construct a template for older brains to aid reporting of clinical and research scans (Wardlaw et al., 2005).

Secondly, to assess lifetime influences on progression of cognitive decline or cerebrovascular disease the cohort could be followed longitudinally. Longitudinal studies minimise cohort effects, and mean that an individual acts as his own baseline, therefore reducing between-subject variance (Ebrahim, 1996). They are, however, more difficult to perform than cross-sectional studies, particularly in studies of ageing, due to loss to follow-up. Given the high attrition rate in an unselected population now aged 80-85, it is unlikely that a follow-up to the Simpson's study would have adequate power to examine influences on cognitive ageing and CVD. An alternative future study is using these data to guide hypotheses for a similar cohort from a different epoch. The Scottish Mental Survey was repeated in 1947 for children born in 1936 (Deary et al., 2004b) and recruitment of 1,000 of these subjects is now underway in Edinburgh. The proportion of hospital births increased with time, with around 75% born at home in 1921 compared with 60% in 1936 (Tait, 1974; General Register Office for Scotland, 1999). Therefore, more participants would have birth data available, and investigation of the relationship between birth weight and cognitive ability in childhood and later life could be repeated in this cohort. As these subjects are now aged around 70, there is the potential for a powerful longitudinal study to follow them prospectively, and neuroimaging (particularly DTI) could be used to track white matter changes and associated cognitive change with time.

The finding of an association between placental size and cerebrovascular disease was novel, and requires to be replicated in larger studies. This could be performed by data linkage of birth records where placental weight is recorded with mortality or morbidity records (e.g.Martyn, 1996). To minimise cohort effects and historical bias placental size could be compared with markers of cerebrovascular risk (e.g. WML, DTI or MT-MRI parameters) at an earlier age, even in childhood (Prayer et al., 2003). However, it is no longer common practice in the UK to weigh the placenta, therefore future studies to investigate placental influence will need to be designed to collect these prospectively, or be based on those placentas that are examined pathologically (those for preterm or low birth weight babies). Animal models of placental dysfunction would allow more detailed study of the biological plausibility

of an influence of placental integrity on cerebrovascular disease (Amiel-Tison et al., 2004).

This cohort is a rich source of data for future analyses on the cognitive abilities, physical characteristics and lifetime socioeconomic environment in relatively healthy older people. Although caution should be exerted in testing hypotheses not identified before the study was designed, new hypotheses derived from the literature could be tested, such as the relationship between cognitive and physical abilities, such as grip strength (Christensen et al., 2000), or the use of alternative markers of atherosclerosis including ECG features (Vinkers et al., 2005). Blood results are available for the testing of hypotheses such as the relationship between HbA_{1c} and cognition (MacLullich, Deary, Starr, Walker, & Seckl, 2004). Samples have also been stored for potential future genotyping to investigate novel candidates for genes for cognitive ageing: in view of the limited power from the current study this will require collaboration with other cohorts (Deary et al., 2004c). There is also the potential for more detailed analysis on markers of social class throughout the life course using parental occupation recorded at the child's birth, parental occupation recorded by the subject, subject's own occupation, as well as markers of childhood deprivation (overcrowding or outside toilet), and periodontal disease, which has been related to atheromatous plaque formation (Desvarieux et al., 2003).

The two main outcomes (cognitive ability and cerebrovascular disease) in this thesis were analysed separately. There is the possibility of performing a complex model looking at the influences on cognitive ability at all stages of life course, possibly with a hierarchical structure, inserting independent variables in batches such as: 1) birth parameters 2) early life influences 3) mid-life socioeconomic circumstances 4) vascular risk factors 5) brain structure. This was not performed on this sample due to the non-significance of early life influences, and low power for >10 variables in a sample size of 110 (Tabachnick, 2000), but future studies with the power to compare the relative importance of these variables could determine which contributes the most to the variance in cognitive ability.

This research crosses numerous disciplines: various branches of medicine (obstetrics, pediatrics, geriatrics, stroke medicine, and neuroradiology), epidemiology, developmental biology and psychology, as well as basic science for mechanistic study. Traditionally, each discipline has acted independently with its own journals and scientific meetings. Paradigm shifts such as the Developmental Origins of Health and Disease are ideal opportunities for interdisciplinary collaboration, (as seen in the establishment of a new Society (International Society for Developmental Origins of Health and Disease, 2005) and such collaboration is essential for the development of understanding of mechanisms, and therefore the potential to affect the incidence of chronic disease. One advantage is the use of techniques traditionally confined to one specialty in others: for example the use of factor analysis to identify latent traits, common in psychology, could be used in the analysis of epidemiological data sets. There is also a need for collaborative research with basic scientists using relevant animal models to allow control of genetic, diet and vascular risk factors and the impact of influencing these individually to be assessed (Langley-Evans, 2004).

8.5 Conclusion

This study of 115 community dwelling people aged 75-81 has shown the importance of a life course approach in studying health and disease in older age, using the examples of cognitive ability and cerebrovascular disease. Distinct effects were found of early life on cognitive ageing and neuroimaging markers of CVD respectively. Studies of cognitive ageing often use outcome measures based on the traditional dichotomy of the presence or absence of disease. An alternative approach would be to study individual differences in more sensitive outcome variables, such as DTI parameters. Studies of these markers of brain ultrastructural change will allow the identification of influences at different points in the lifespan, from preconceptual genetic and epigenetic factors, through prenatal nutritional and hormonal effects, to the influences of the environment from birth to old age. It is important not only to consider the absolute values of birth measurements, but to investigate the mechanisms whereby these are affected. The use of data from early life emphasises the importance of considering prior ability or health when studying older people.

Through multidisciplinary collaboration there is now potential to identify targets from earlier life to improve the health and function of older people.

9 Appendix

9.1 Publications arising from this thesis

Shenkin SD, Bastin ME, MacGillivray TJ, Deary IJ, Starr JM, Rivers CS, Wardlaw JM. Cognitive Correlates of Cerebral White Matter Lesions and Water Diffusion Tensor Parameters in Community Dwelling Older People. *Cerebrovascular Diseases* 2005; **20**: 310-318.

Shenkin SD, Starr JM, Deary IJ. Birth Weight and Cognitive Ability in Childhood: a Systematic Review. *Psychological Bulletin* 2004; **130 (6):** 989–1013.

Shenkin SD, Bastin ME, MacGillivray TJ, Deary IJ, Starr JM, Wardlaw JM. Childhood and current cognitive function in healthy 80-year-olds: a DT-MRI study. *Neuroreport* 2003; **14 (3):** 345-351

Shenkin SD, Starr JM, Pattie A, Rush MA, Whalley LJ, Deary IJ. Birth weight and cognitive function at age 11 years: results from the Scottish Mental Survey 1932. *Arch Dis Child* 2001; **Sep; 85(3)**:189-96.

Original Paper

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Cognitive Correlates of Cerebral White Matter Lesions and Water Diffusion Tensor Parameters in Community-Dwelling Older People

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Key Words
Cognitive ageing · White matter · Diffusion tensor magnetic resonance imaging

Abstract
Background: The biological basis of cognitive ageing is unknown. One underlying process might be disruption of white matter tracts connecting cortical regions. White matter lesions (WML) seen on structural MRI may disrupt cortical connections, but diffusion tensor MRI (DT-MRI) parameters – mean diffusivity (<D>) and fractional anisotropy (FA) – may reflect more subtle changes in white matter integrity. Here the relationships between WML load, DT-MRI parameters and cognition in a large cohort of elderly subjects with a very narrow age range were investigated. ***Methods:*** 105 community-dwelling volunteers underwent MRI and neuropsychological assessment. Seventy-two (68.6%) were female, and their mean age was 78.4 (SD 1.5) years. Scans were rated for WML load. <D> and FA were measured from regions of interest in normal-appearing frontal and occipital white matter, and centrum semiovale. ***Results:*** <D> and FA differed significantly among the three brain regions studied ($p \ll 0.01$). <D> increased with age ($r = 0.22$ to 0.35, $p < 0.03$), and was negatively correlated with FA ($r = -0.20$ to -0.51, $p < 0.05$) in all three regions. There was a trend towards increased WML load correlating with poorer cognitive function, and this was statistically significant for the Mini-Mental State Examination ($\rho = -0.23$, $p = 0.02$). <D> was generally negatively correlated with cognitive test score, and FA was positively correlated. This pattern was more consistent for <D> than for FA, and particularly for verbal fluency (<D>: $r = -0.22$ to -0.27, $p < 0.03$), which measures executive function. ***Conclusions:*** DT-MRI parameters, in particular <D>, are sensitive to early ultrastructural changes underlying cognitive ageing. Executive function may be the cognitive domain most sensitive to age-related decline in white matter tract integrity.

Introduction

Cognitive abilities change with age, but the biological bases of these changes are not well understood [1, 2]. White matter lesions (WML) increase in prevalence with age, and may have a vascular aetiology [3]. Increased WML load correlates with cognitive impairment [4, 5], but studies disagree as to the size of the effect and the cognitive domains involved [6]. This may be due to differences in study design, the multifactorial aetiology of WML, and difficulty in coding WML, particularly the possible insensitivity of WML rating scales to subtle early pathology [6]. Since disruption of white matter tracts connecting cortical regions may underlie cognitive decline [7, 8], there is a need for more sensitive measures of white matter integrity. This is particularly important if subtle changes are to be detected early in the disease process when it is more likely that interventions to slow or halt cognitive decline would be effective.

One such technique is diffusion tensor MRI (DT-MRI), which provides a non-invasive method of investigating the ultrastructure of the brain, and may be sensitive to age-related white matter deterioration [8, 9]. Using this modality, the diffusion of water molecules in vivo can be characterised by two parameters, namely mean diffusivity (<D>), which measures the magnitude of water diffusion, and fractional anisotropy (FA), which indicates the directional coherence of diffusion predominantly in the extracellular space [10, 11]. The presence of axonal membranes and myelin means that water molecules diffuse preferentially in parallel with the long axes of tightly packed axonal bundles, rather than across them [10]. These diffusion parameters are therefore thought to provide useful markers of white matter fibre bundle integrity, with low values of <D> and high values of FA indicating intact healthy neurons [8–11].

Several studies have found that <D> increases and FA decreases with age [12–17]. These changes occur in normal ageing, in parallel with changes in cognition, and therefore provide a plausible biological explanation for cognitive ageing [1, 2]. Four studies have explicitly examined the relationship between cognition and DT-MRI data in older people without clinical disease, providing most evidence for a relationship between DT-MRI parameters in frontal regions and executive function [8, 18–21]. However, these studies all have small numbers of subjects (17–31) and large age ranges (e.g. 19–70 [18] and 56–85 [8] years). There is therefore a need for more adequately powered studies with subjects of a narrow age range to investigate further whether reduced white matter integrity is one of the foundations of individual differences in cognitive ageing.

In this study, the relationships between cognitive ability and both WML load and DT-MRI parameters were investigated in a large cohort of community-dwelling older people with a narrow age range. WML scales were used to score lesions visible on structural MRI scans, while DT-MRI parameters were measured in normal-appearing white matter to characterise more subtle changes in white matter integrity. It was hypothesised that WML load and DT-MRI parameters have associations with cognition, with a higher WML score and increased <D> and decreased FA correlating with worse cognitive function. Furthermore, based on the results of previous smaller studies, it was hypothesised that relationships between DT-MRI parameters and cognition are strongest in frontal regions, and with tests of executive function.

Methods

Subjects

One hundred and fifteen volunteers, born in Edinburgh Hospitals between 1921 and 1926, were recruited from the community by invitation and local media appeal. The only exclusion criteria, apart from normal contraindications to MRI, were severe physical or mental illness that would have made participation in the study inappropriate. This was determined by the individuals or their general practitioner after hearing a description of the study. All subjects provided information on previous medical history including vascular risk factors (diabetes, hypertension, cardiovascular disease) and smoking history. Each underwent neurological and cognitive testing on one day, and carotid Doppler ultrasound imaging and the MRI examination described below at a subsequent attendance. All subjects provided informed consent, and the local research ethics committee approved the protocol.

Cognitive Tests

Prior cognitive ability was estimated using the National Adult Reading Test (NART) [22] – the ability to correctly read 50 irregularly pronounced words. Global cognitive function was assessed using the Mini-Mental State Examination (MMSE) [23]. Executive function was assessed with verbal fluency using the Controlled Word Association Test [24] – the total number of words volunteered within 1 min starting with the letters C, then F then L. Verbal reasoning was assessed using a version of the Moray House Test No. 12 [1], and non-verbal reasoning using Raven's Progressive Matrices [25]. Verbal memory was assessed using the logical memory (immediate plus delayed) subtest of the Wechsler Memory Scale – Revised [26]. The tests were administered by a trained research fellow (S.D.S.), blinded to all imaging data.

MRI Scanning

All MRI data were obtained using a GE Signa LX 1.5 T (General Electric, Milwaukee, Wisc., USA) clinical scanner, equipped with a self-shielding gradient set (22 mT/m maximum gradient strength) and manufacturer-supplied 'birdcage' quadrature head coil. The MRI examination consisted of standard structural imaging, a coronal three-dimensional fast spoiled gradient echo T_1-weighted volume sequence with whole brain coverage (TR 7.3 ms, TE 3.1 ms, TI 400 ms, flip angle 20°, slice thickness 1.7 mm, no interslice gap, FOV 240 × 240 mm, matrix 256 × 256), and a previously described DT-MRI protocol based on spin-echo echo-planar (EP) imaging [19]. The structural imaging consisted of axial T_1-weighted spin-echo, axial T_2-weighted fast spin-echo (TR 6,300 ms, TE 102 ms, slice thickness 5 mm, interslice gap 1.5 mm, FOV 240 × 240 mm, matrix 256 × 256) and axial FLAIR fast spin-

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echo imaging (TR 9,000 ms, TE 140 ms, TI 2,200 ms, slice thickness 5 mm, interslice gap 1.5 mm, FOV 240 × 240 mm, matrix 256 × 224). The duration of the examination was approximately 40 min.

In the DT-MRI protocol, sets of axial EP images (b = 0 and 1,000 s/mm^2) were collected with diffusion gradients applied sequentially along six non-collinear directions. Five acquisitions consisting of a baseline T_2-weighted EP image and six diffusion-weighted EP images, a total of 35 EP images, were collected per slice position. The acquisition parameters for the EP imaging sequence were 21 axial slices of 5 mm thickness and 1.0 mm slice gap, an FOV of 240 × 240 mm, an acquisition matrix of 128 × 128 (zero filled to 256 × 256), a TR of 10 s and a TE of 98.8 ms.

Image Processing

From the DT-MRI data, the apparent diffusion tensor of water (D) was calculated in each voxel from the signal intensities in the component EP images [10]. Maps of <D> and FA for each subject were generated on a voxel-by-voxel basis from the sorted eigenvalues of D and converted into Analyze (Mayo Foundation, Rochester, Minn., USA) format.

Regions of interest (ROI) were placed in frontal and occipital white matter and centrum semiovale using the T_2-weighted EP images, avoiding areas with WML, following an approach described previously [19]. In this method, values of <D> and FA for normal-appearing frontal and occipital periventricular white matter were obtained from multiple small circular (69 voxels, volume 303 mm^3) ROI placed near the anterior and posterior horns of the lateral ventricles. Several larger, oval ROI (typically 500 voxels, volume 2,197 mm^3) were also placed in normal-appearing centrum semiovale. Partial volume effects were minimised by placing the ROI at least 3 voxels from both the edge of the ventricles and abnormally appearing white matter. Since the T_2-weighted EP images and the DT-MRI parametric maps were by definition coregistered, this allowed <D> and FA values to be measured simultaneously in the ROI. Mean <D> and FA values were obtained from the average of the left and right ROI measurements made in at least two appropriate slices for each region in every subject. The observer (T.J.M.) was blinded to the clinical status and cognitive function of participants and the purpose of the study.

Blinded to his original ROI selection, the observer also performed an assessment of intrarater reliability of ROI placement and editing by repeating the above analysis in 10 subjects chosen at random from the study cohort.

Cerebrovascular Disease, WML Load and Brain Volumes

Each scan was examined for evidence of prior cerebrovascular disease, with the presence of infarct or haemorrhage noted. Each scan was quantified independently for WML load on the T_2-weighted and FLAIR images using a recognised rating scale (Fazekas scale) [27]. This rates WML separately for periventricular hyperintensities (PVH) and deep white matter hyperintensities (DWMH) providing a score of 0–3 for each. This scale was used because it was found to be appropriate for capturing a broad range of degrees of white matter abnormalities from mild to severe [4]. The rater (J.M.W.) is an experienced neuroradiologist who was blinded to all cognitive and DT-MRI data. Whole brain volumes were independently measured (C.S.R.) from the T_1-weighted volume imaging data using a previously described semi-automated method [28]. The whole brain volume included all brain parenchymal tissue, with the brain separated from the spinal cord at the most inferior position of the cerebellum.

Statistical Analyses

Differences in DT-MRI parameters between frontal and occipital white matter, and centrum semiovale were tested using repeated-measures general linear modelling (one-factor within-subject ANOVA), and where differences were found, these were investigated using Bonferroni-adjusted pairwise comparisons. Bivariate correlations were used to investigate the relationship between: (a) DT-MRI parameters and age (Pearson's r), (b) WML and age (Spearman's ρ), (c) DTI parameters and WML load (Spearman's ρ), (d) cognition and WML load (Spearman's ρ), (e) cognition and DT-MRI parameters (Pearson's r) and (f) whole-brain volume and DT-MRI parameters (Pearson's r). The influence of potential confounders on the relationship between cognition and DT-MRI was investigated using partial correlation. Sex differences in DT-MRI parameters were tested using Student's t test, and in WML using the Mann-Whitney U test. Analysis of covariance was used to test whether both age and sex influenced <D>. The importance of a history of vascular risk factors on DT-MRI parameters was tested using one-way ANOVA. All analyses were performed using SPSS version 12 (SPSS Inc., Chicago, Ill., USA).

Data Reduction

All cognitive tests were positively intercorrelated (r = 0.08 to 0.66), and principal component analysis was therefore used to derive a general cognitive factor (*g*) from the tests of more fluid ability, i.e. verbal fluency, Raven's Progressive Matrices, Moray House Test and logical memory subtest. The first unrotated principal component accounted for 50.7% of the total variance. Each subject was given a score on this general cognitive factor, in addition to NART and MMSE scores. Correlations between brain MRI parameters and these scores were examined initially, and then the associations with individual test scores were calculated.

Results

Of the 115 subjects originally recruited, 110 completed the MRI examination (4 aborted due to claustrophobia and 1 for positional vertigo). The structural MRI scans were examined by a neuroradiologist (J.M.W.) to exclude silent pathology (1 subject had a large incidental meningioma). There were technical problems with the DT-MRI acquisition in a further 4 subjects, so that usable DT-MRI data were obtained from a total of 105 people. Of these subjects, 72 (68.6%) were female, and their mean age was 78.4 years (SD 1.5, range 75.5–81.5). There were no frontal white matter <D> and FA values for 1 participant, and no occipital white matter measures for another, due to inability to place ROI in normal-appearing tissue. Vascular risk factors and whole brain volume are shown in table 1. Results for the cognitive tests are shown in table 2. Missing data were due to deafness, visual impairment or incomplete tests. The cognitive tests have a normal distribution, except for MMSE, which shows a ceiling effect.

Table 1. Descriptive statistics for vascular risk factors and whole brain volume

	n	%
History of hypertension	48	45.7
History of CVD	35	33.3
History of stroke/TIA	10	9.5
History of NIDDM	6	5.7
Current smoker	8	7.6
Ex-smoker	49	46.7
Carotid artery stenosis >60%		
Right	7	6.7
Left	6	5.7
MRI		
Infarct	8	7.7
Lacunar infarct	2	1.9

	Mean	SD	Range
Systolic BP, mm Hg	159.1	26.2	103–238
Diastolic BP, mm Hg	79.2	12.8	54–124
BMI, kg/m^2	27.3	4.0	18.7–40.8
Whole brain volume, cm^3	1,136.5	98.6	947.4–1,405.3

CVD = Cardiovascular disease (angina or myocardial infarct); TIA = transient ischaemic attack; NIDDM = non-insulin-dependent diabetes; BMI = body mass index.

MRI Results

Rating on the Fazekas scale was positively skewed for both PVH (range 1–3, median 1) and DWMH (range 0–3, median 1), indicating a low WML load in the majority. There was no significant sex difference in WML score and no significant increase in WML scores with age.

Table 3 shows <D> and FA values for frontal, occipital and centrum semiovale regions. There were statistically significant differences between the three regions for <D> [$F_{(2, 204)} = 286.0$, $p \ll 0.01$] and FA [$F_{(2, 204)} = 178.8$, $p \ll 0.01$]. Bonferroni-adjusted pairwise comparisons showed that <D> was highest and FA lowest in the frontal region.

The intrarater reliability analysis indicated excellent reproducibility of all ROI measurements, with the SD of the difference between repeated measurements of <D> and FA being 8 × 10^{-6} mm^2/s (mean of measurements 774 × 10^{-6} mm^2/s) and 0.02 (mean 0.37), respectively. This yielded coefficients of variation of 1.0% for <D> and 4.6% for FA, which compares well with previous ROI measurements in older subjects [8].

<D> correlated significantly with age in all regions (frontal white matter: r = 0.22, p < 0.03; occipital white matter: r = 0.35, $p \ll 0.01$; centrum semiovale: r = 0.29,

Table 2. Descriptive statistics for cognitive test score results

Test	Patients	Mean score	SD	Range	Max possible
NART (positive score)	105	30.1	7.8	11–44	50
MMSE	102	28.3	1.4	24–30	30
Verbal fluency (total)	105	37.3	12.1	15–78	–
Raven's Progressive Matrices	102	30.9	8.1	12–51	60
Moray House Test	99	57.6	8.4	30–74	76
Logical memory subtest (total)	104	33.0	11.6	6–74	100

Table 3. Mean and SD values of DT-MRI parameters in normal-appearing white matter in 72 female and 33 male volunteers with a mean age of 78.4 years

Region	Mean diffusivity, × 10^6 mm^2/s			Fractional anisotropy		
	male	female	total	male	female	total
Frontal WM	854 ± 54	833 ± 35	840 ± 43	0.31 ± 0.03	0.30 ± 0.03	0.30 ± 0.03
Occipital WM	771 ± 45	756 ± 31	761 ± 37	0.42 ± 0.04	0.42 ± 0.05	0.42 ± 0.04
Centrum semiovale	784 ± 58	761 ± 33	768 ± 44	0.40 ± 0.06	0.39 ± 0.06	0.39 ± 0.06

Table 4. Correlations between WML Fazekas score and cognitive ability (Spearman's ρ)

	Periventricular hyperintensities		Deep white matter hyperintensities	
	ρ	p	ρ	p
Hypothesis	negative		negative	
NART	–0.03	0.79	–0.04	0.65
MMSE	–0.23*	0.02*	–0.10	0.33
g	–0.13	0.21	–0.04	0.67
Verbal fluency	–0.09	0.38	–0.02	0.80
Raven's Progressive Matrices	–0.14	0.15	–0.08	0.42
Moray House Test	–0.15	0.14	0.00	1.00
Logical memory subtest	–0.02	0.84	–0.04	0.72

* $p < 0.05$.

Table 5. Correlations between DT-MRI parameters and cognitive ability

	Mean diffusivity						Fractional anisotropy					
	frontal WM		occipital WM		centrum semiovale		frontal WM		occipital WM		centrum semiovale	
	r	p	r	p	r	p	r	p	r	p	r	p
Hypothesis	negative		negative		negative		positive		positive		positive	
NART	–0.07	0.51	–0.08	0.41	–0.10	0.31	0.04	0.68	0.11	0.26	0.09	0.34
MMSE	–0.18	0.07	–0.15	0.13	–0.21*	0.04*	0.07	0.51	0.02	0.84	–0.02	0.88
g	–0.08	0.44	–0.18	0.08	–0.15	0.14	–0.00	0.97	0.13	0.20	0.14	0.15
VF	–0.25*	0.01*	–0.27*	0.01*	–0.22*	0.03*	–0.07	0.49	0.25*	0.01*	0.07	0.46
RPM	–0.06	0.58	–0.09	0.37	–0.10	0.30	–0.02	0.83	0.02	0.86	0.08	0.39
MHT	–0.09	0.40	–0.21*	0.04*	–0.14	0.16	0.13	0.20	0.17	0.09	0.11	0.28
LM	0.02	0.82	–0.06	0.56	–0.12	0.23	–0.02	0.82	–0.08	0.44	0.12	0.23

All correlations are assessed using Pearson's r except MMSE where Spearman's ρ is used. * $p < 0.05$. VF = Verbal fluency (Controlled Word Association Test); RPM = Raven's Progressive Matrices; MHT = Moray House Test; LM = logical memory subtest.

$p \ll 0.01$), but there was no significant association between FA and age. Men had higher <D> than women (frontal white matter: $t = 2.08$, $p = 0.04$; occipital white matter: $t = 1.73$, $p = 0.09$; centum semiovale: $t = 2.08$, $p = 0.04$), but there were no significant sex differences for FA. Men were significantly older than women ($t = 2.44$, $p = 0.02$). Analysis of covariance was used to test whether both age and sex influenced <D>. With both age and sex in the model, only age contributed to the variance in <D>, i.e. there was no sex difference in <D> when age was taken into account.

Across all subjects and correcting for age, <D> and FA were significantly negatively correlated in all three regions (frontal white matter: $r = -0.20$, $p < 0.05$; occipital white matter: $r = -0.51$, $p \ll 0.01$; centrum semiovale: $r = -0.38$, $p \ll 0.01$).

Higher scores on WML load were associated with higher <D> in frontal white matter ($\rho_{PVH} = 0.31$, $p < 0.01$; $\rho_{DWMH} = 0.29$, $p < 0.01$) and centrum semiovale ($\rho_{PVH} = 0.35$, $p < 0.01$; $\rho_{DWMH} = 0.26$, $p < 0.01$) regions, but not occipital white matter or FA in any region.

MRI Parameters and Cognition

Table 4 shows correlations between WML load and cognitive test scores. The correlations were all in the expected direction, namely higher WML score being associated with poorer cognitive test result, with the association between MMSE and PVH reaching conventional statistical significance ($\rho = -0.23$, $p = 0.02$).

Correlations between DT-MRI parameters and cognitive tests are shown in table 5. Generally, as hypothesised, <D> was negatively correlated with cognitive test results, and FA was positively correlated. In the three correlations for broad cognitive ability (NART, MMSE and *g*), conventional significance was reached for MMSE in centrum semiovale <D> ($\rho = -0.21$, $p = 0.04$). When the relationship between DT-MRI parameters and verbal fluency alone was considered, there was a relationship between <D> and verbal fluency in all brain areas ($r = -0.22$ to -0.27), and between FA and verbal fluency in the occipital region ($r = 0.25$, $p = 0.01$).

To assess the role of potential confounders, namely WML load, whole brain volume, age, sex and prior ability (estimated by NART), partial correlation was performed on the cognitive tests and DT-MRI parameters controlling for these variables. All associations were attenuated, but the associations with verbal fluency remained (<D> frontal white matter: $r = -0.21$, $p = 0.05$; <D> occipital white matter: $r = -0.23$, $p = 0.03$; <D> centrum semiovale: $r = -0.14$, $p = 0.19$; FA occipital white matter: $r = 0.19$, $p = 0.08$). None of the other cognitive tests, including the g factor, had a significant association with DT-MRI parameters when corrected for these potential confounders. Analyses were repeated excluding 10 subjects with prior infarction on MRI. All associations were attenuated, but the association with verbal fluency remained statistically significant (<D> frontal white matter: $r = -0.21$, $p = 0.04$; <D> occipital white matter: $r = -0.22$, $p = 0.04$; <D> centrum semiovale: $r = -0.19$, $p = 0.06$; FA occipital white matter: $r = 0.23$, $p = 0.03$). There were no significant correlations between whole brain volume and DT-MRI parameters ($r = -0.03$ to 0.16, all p values > 0.1).

Vascular Risk Factors

Since WML are thought to have a vascular aetiology, the influence of vascular risk factors on DT-MRI parameters was investigated. The DT-MRI parameters were compared between those with or without vascular risk factors or a diagnosis of vascular disease using ANOVA. There were no significant differences in cognitive test scores for those with or without a history of diabetes, hypertension, and cardiovascular or cerebrovascular disease. For DT-MRI parameters, those with a history of hypertension had higher <D> frontally [$F_{(1, 102)} = 4.81$, $p = 0.03$] and those with a history of cerebrovascular disease had higher <D> in all areas [frontal white matter: $F_{(1, 102)} = 8.9$, $p \ll 0.01$; occipital white matter: $F_{(1, 102)} = 12.0$, $p \ll 0.01$; centrum semiovale: $F_{(1, 100)} = 4.1$, $p < 0.05$] and lower FA in frontal and occipital regions [frontal white matter: $F_{(1, 102)} = 5.1$, $p = 0.03$; occipital white matter: $F_{(1, 102)} = 7.7$, $p < 0.01$]. There were no differences in DT-MRI parameters for those with or without an infarct on MRI. There were no statistically significant associations between DT-MRI parameters and blood pressure (BP) or body mass index, and no significant differences between current, ex- and non-smokers.

Discussion

This is the largest study to date in which relationships between WML load, water diffusion parameters and cognitive function have been investigated. A major strength of this study is the inclusion of a cohort of community-dwelling older subjects with a narrow age range, namely 75–81 years, which is significantly older than the subjects included in most published studies. Since the main correlate with cognitive function is normally age, studying a cohort with a narrow age range allows the relationship between brain MRI data and individual differences in cognitive ability to be investigated [29].

These data therefore add to the current literature in four main areas. Firstly, the use of a sample from the community, whose only exclusion criteria were severe physical or mental illness, means that the values for <D> and FA can be used as reference values for typical older people. For example, <D> is generally higher, particularly frontally, than in previously published cohorts, which used hospital-based [14] or younger [12, 13, 30] subjects. This is consistent with changes described with increasing age. The FA values are very similar to those published for healthy middle-aged subjects [9, 30] except for reduced FA in frontal regions. This may be due to ageing changes disproportionately affecting the frontal lobes [2, 14, 17]. The fact that, even within a six-year age band, <D> changes with increasing age is important when comparing cohorts of people. Cross-sectional studies that compare old with young groups should consider differences within, as well as between these groups. The fact that there were significant differences between brain regions, with frontal white matter having the highest <D> and lowest FA, also shows the importance of ROI selection.

Secondly, further data are presented on the associations between WML load and cognition, using a group of people with relatively low WML load and high cognitive ability. Significant associations have been found previ-

ously in the largest studies which include a wide range of WML loads and cognitive ability [4, 5]. The main cognitive deficits were in tasks of processing speed, executive function, memory and global cognitive function rather than general intelligence [6]. The current finding of a trend towards correlations between increased WML load and poorer cognitive function is therefore consistent with the literature [6]. However, the current study size was inadequate to detect statistical significance in correlations with an effect size of less that 0.2. Nevertheless, statistical significance was reached for WML load and MMSE, a crude, but widely used test of global cognitive function. This provides further evidence that increased WML load is associated with impaired cognitive ability.

Thirdly, the cognitive correlates of both WML and DT-MRI parameters were considered in the same study. Some studies relating DT-MRI data to cognitive ability have not accounted for WML in their analyses [18, 20]. Increased <D> and decreased FA have been shown both within WML, and in surrounding normal-appearing white matter [31, 32]. Thus, changes detected by DT-MRI are not restricted to areas that are abnormal on T_2-weighted MRI, and it is important to consider WML burden in DT-MRI studies of older people. Previous studies have found statistically significant associations between (1) <D> and cognition: anterior white matter <D> with executive function [8], and centrum semiovale <D> with MMSE [19], and (2) FA and cognition: frontal white matter FA with executive function [19] and verbal reasoning [19]; middle white matter FA with verbal fluency [8], and centrum semiovale FA with prior IQ and verbal reasoning [19]. In the current well-powered study, although there was a trend in the expected direction, the only statistically significant association between white matter water diffusion parameters and three broad measures of cognitive ability (NART, MMSE and *g*) was for centrum semiovale <D> and MMSE. Thus, as the sample sizes have increased, the effect size of the correlation has decreased (from a correlation coefficient of 0.4 to 0.9 [8, 18–22] to 0.1 to 0.2 in this study), implying that the true effect is nearer to that found here. However, the most consistent and strongest association between cognitive tests and DT-MRI parameters was between verbal fluency, a non-specific measure of executive function, and <D>. Interestingly, this negative correlation was present in all regions studied, not just the frontal region. This agrees with a previous small DT-MRI study [8] and neuroimaging evidence that suggests that executive functions are more widely distributed throughout the brain than previously thought [33]. These findings indicate that executive function may be the cognitive domain most sensitive to subtle, diffuse, age-related deterioration in white matter integrity. Furthermore, the possibility of these results being prone to type I error is reduced by the large number of subjects, indicating tight confidence intervals around the coefficient, combined with the fact that the significant correlations are not randomly spread throughout the matrix. A Bonferroni correction for multiple testing is not appropriate here, as the variables are intercorrelated [34].

Finally, since WML are thought to have a vascular aetiology [3], the influence of vascular risk factors on DT-MRI parameters was also considered. Those subjects with higher WML load had higher <D> in normal-appearing white matter than those with fewer WML, which is consistent with previous studies [31, 32]. This suggests that DT-MRI changes might detect pathologic white matter damage at an early stage, thereby allowing interventions to prevent progression to WML. Potential targets for such interventions include vascular risk factors. Significant differences were found in DT-MRI parameters between those with and without a history of vascular disease or hypertension. Those with hypertension had higher <D>, consistent with the literature showing hypertension as the vascular risk factor with the most robust association with WML [35]. Those with a history of cerebrovascular disease, also known to be associated with WML [35, 36], had higher <D> and lower FA. Significant negative correlations were also observed between <D> and FA for all three brain regions studied in this cohort. Such correlations have been reported previously by Pfefferbaum and Sullivan [15] in the genu, splenium and centrum semiovale of 64 normal volunteers aged 23–85 years, and by Head et al. [14] in frontal, temporal, parietal and occipital white matter regions in 25 young adults aged 19–28 years, 25 non-demented older adults aged 69–88 years and 25 age-matched older adults with Alzheimer-type dementia. In both studies, the correlations were strongest for the older subjects, especially the Alzheimer dementia group. These data suggest that increasingly significant correlations between <D> and FA are indicative of pathological change in white matter, with cerebrovascular disease being one possible mechanism in normal ageing [14]. Countering the argument that <D> and FA can be used as measures relating to cerebrovascular disease is the finding that measured BP (arguably more sensitive than self-reported history) was not related to DT-MRI. However, BP may have been affected by treatment or attendance at the clinic. DT-MRI parameters are known to change in the evolution of stroke [37], and cerebrovascular disease is associated with cognitive impairment [38]. Therefore, using DT-MRI to investigate relationships between vascular risk factors, cerebrovascular disease, cognition and white matter integrity is a promising area for future research.

The current study has several potential weaknesses. The first of these is the use of a volunteer community-dwelling sample, which raises the possibility of selection bias. In general, study volunteers tend to be of higher socio-economic status and better educated than non-participants [1, 5]. This may lead to a restricted range of results, and thus a conservative estimate of any association. It is also possible that subjects with an underlying illness were more (or less) likely to volunteer, due to the potential for medical assessment, although we found a prevalence of vascular risk factors similar to studies where subject selection attempted to be representative of the population [e.g. 35]. These potential biases should be considered when extending these results to other samples and populations.

The second potential weakness of this study is the use of ROI methodology. Although we employed an ROI method previously used in studies of ageing and cognition [19, 32, 38], the subjective nature of ROI placement remains a problem in the study of normal subjects. This issue principally affects the measurement of FA, since even small variations in ROI location will produce significantly different results depending on where the ROI is placed relative to the white matter tracts [15]. <D> is less sensitive to these effects, which may explain why our results were more consistent for <D> than FA. This problem could be addressed by defining the ROI co-ordinates in Talairach space and determining the corresponding location in the subject's native space [39], if registration of elderly brains to a standard template can be performed accurately. Alternatively, segmenting the brain's entire white matter volume would allow histogram measurements of <D> and FA to be obtained from large areas of white matter without subjective placement of ROI [8, 13, 40]. However, the presence of WML makes both approaches far more problematic than in younger people. Further work is required to determine what the optimum method is for measuring water diffusion parameters reproducibly in the brains of older people with atrophy and white matter disease.

Conclusions

In this study, relationships between cognitive ability and both WML load and DT-MRI parameters in a large group of community-dwelling older people aged between 75 and 81 years were investigated. There was a trend towards increased WML load correlating with poorer cognitive function, and this trend was significant for the MMSE. Correlations were found between DT-MRI parameters and cognitive ability, specifically verbal fluency and <D>. This indicates that executive function may be the cognitive domain most sensitive to age-related decline in white matter tract integrity. DT-MRI may therefore be a useful tool to investigate the anatomy of early cognitive impairment in normal older people.

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Birth Weight and Cognitive Ability in Childhood: A Systematic Review

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Individual differences in cognitive ability may in part have prenatal origins. In high-risk (low birth weight/premature) babies, birth weight correlates positively with cognitive test scores in childhood, but it is unclear whether this holds for those with birth weights in the normal range. The authors systematically reviewed literature on the relationship between normal birth weight (more than 2,500 g) and childhood intelligence in term (37–42-week gestation) deliveries. Six studies met the inclusion criteria, and the authors present a comprehensive narrative review of these studies. There was a small, consistent, positive association between birth weight and childhood cognitive ability, even when corrected for confounders. Parental social class accounted for a larger proportion of the variance than birth weight, and these 2 variables were largely independent.

Individual differences in human intelligence are the product of both genetic and environmental influences. Environmental influences are of particular interest in that they may be more readily modifiable. Environmental factors begin affecting development long before birth, while the fetus is still developing in the womb. The fact that the prenatal environment may have long-term effects on individual outcomes has recently gained attention in the medical and epidemiological literature in the area known as fetal origins of adult disease (Barker, 1998), according to which events in utero, possibly maternal malnutrition, program the fetus to develop differently, and this is reflected in relatively low birth weights (even those within the normal range). Babies with lower birth weights have increased risks of Type 2 diabetes, coronary heart disease, and osteoporosis in adult life, particularly if they are born into an environment of nutritional excess (Barker, 1998). This had led to a shift in focus in the etiology of disease from adult lifestyle to accumulation of risk throughout the life course, beginning before birth. Thus, there is currently much interest in birth weight and other perinatal measures as possible predictors of various outcomes in later life. One such outcome, important in the field of psychology, is cognitive ability (intelligence) differences, and in this review we consider the relationship between birth weight and intelligence.

Birth weight is necessarily a crude summary of multiple influences on the developing fetus (Kline, Stein, & Susser, 1989). To distinguish between growth appropriate for gestational age and growth restriction, birth weight should be corrected for gestational age. Ideally, birth weight should also be corrected for parental size (Robinson, Moore, Owens, & McMillan, 2000), but few studies include such data. Classification merely by birth weight does not provide information about the etiology of low birth weight. It will not distinguish a sudden insult resulting in impaired growth from slow growth since conception (Rasmussen, 2001). Notwithstanding these caveats, birth weight itself remains a useful, albeit crude, measure of development and a significant correlate of adult health differences.

Low Birth Weight and Intelligence

Much of the research relating perinatal factors to intelligence has focused on infants at high risk of poor outcomes, particularly those who are born prematurely (before 37 weeks) or have low birth weights (i.e., below 2,500 g). These children represent only a tiny proportion of all births, but identifying them is important because, whatever the cause of their size, they are at increased risk of morbidity and mortality (Barker, 1998; Rasmussen, 2001).

Concern about the high mortality and morbidity of low birth weight babies led to interest in the cognitive outcomes of this high-risk group. There is now a sizable literature comparing the performance of low birth weight (as well as very low birth weight and extremely low birth weight) children and control children of normal birth weight (i.e., more than 2,500 g).

A meta-analysis of 80 studies conducted during the 1980s analyzed the cognitive outcomes of low birth weight infants at the ages of 2 to 10 years (Aylward, Pfeiffer, Wright, & Verhulst, 1989). Cognitive ability (IQ) was determined from various tests, most frequently the Bayley Scales of Infant Development, the Stanford-Binet Intelligence Scale, or the Wechsler Intelligence Scale for Children (WISC). Methods of assessing developmental quotient (DQ) were not reported. Mean IQ/DQ scores were 97.77 (SD = 6.19) for low birth weight children and 103.78 (SD = 8.16) for controls (Cohen's d = .59). The conclusion was that there was a "statistically significant but perhaps not clinically significant" (Aylward et al., 1989, p. 520) difference between low birth weight babies and controls. The studies analyzed were heterogeneous in terms of participants recruited, methods used for assessment and analysis, consideration of confounding variables, and outcome measures used. The authors therefore suggested caution in interpreting their results, along with the need for an international conference on developmental follow-up to address these issues.

These issues have not yet been resolved (Aylward, 2002b). A nonsystematic review of 9 studies focusing on children up to the age of 7 years (Grantham-McGregor, 1998) showed a difference in IQ between small for gestational age babies and controls, the size of which decreased with age. A review of 15 studies of outcomes in adolescence and adulthood (Hack, 1998) concluded that there was "overall normal intelligence with a trend to lower scores among IUGR [intrauterine growth retardation] subjects . . . there is no consistent evidence of a detrimental effect of IUGR on the mental and behavioural outcomes of adolescents or adults" (p. S69). Effect sizes were not reported. This review concluded that the social environment was more influential than intrauterine growth failure.

Ornstein, Ohlsson, Edmonds, and Asztalos (1991) reviewed 25 studies pertaining to various outcome measures among babies weighing less than 1,500 g and concluded that these children have significantly lower IQs than control children, although their means still fall within the age-appropriate range. They found that environmental influences, when measured, were often the most important predictors of long-term outcomes. Only summary outcomes were included; test results and effect sizes were not reported. These reviewers and others (Joseph & Kramer, 1996; Rasmussen, 2001) reiterated the concerns of Aylward et al. (1989) regarding the need for rigorous methodologies in future studies.

In a meta-analysis with stringent inclusion criteria, Bhutta, Cleves, Casey, Cradock, and Anand (2002) analyzed 15 studies of premature babies in which cognition was tested at school age and compared with that of matched control children. Controls had significantly higher cognitive scores than children who were born preterm (weighted mean difference = 10.9, 95% confidence interval [CI] = 9.2, 12.5). Group-level data showed that the mean cognitive scores of preterm-born case participants and term-born controls increased as their birth weight increased (R^2 = .51, p < .001) and as their gestational age increased (R^2 = .49, p < .001).

It therefore seems that, within the restrictions imposed by study designs (randomized controlled trials designed to induce low birth weight or prematurity would be unethical), children who are both premature and have low birth weights perform less well on psychometric tests than their peers. The relationship is probably stronger for premature babies than for low birth weight babies. Within the low birth weight group, lighter babies perform less well, and overall low birth weight babies perform less well than those in the normal range (Bhutta et al., 2002). The effect size is small to medium, and therefore the small improvements in birth weight or prematurity that might be achieved by medical interventions are more likely to have an impact at the population rather than individual level.

Premature and low birth weight babies are of interest to researchers because these children often have long-term contact with health services, with financial implications (Petrou, Sach, & Davidson, 2001). Furthermore, advances in medical technology have led to increases in the proportions of such births. In the United States, 11.6% of births in 2000 were premature and 7.6% of babies had low birth weights (Martin, Hamilton, Ventura, Menacker, & Park, 2002), whereas in Scotland, 7.5% of births were premature and 2.8% of babies had low birth weights (Information and Statistics Division, Common Services Agency, 2003). Thus, in these industrialized nations, most births neither are premature nor involve low birth weight.

Normal Birth Weight and Intelligence

The research showing that low birth weight or premature babies, or both, have relatively lower intelligence test scores than controls, and in particular the suggestion that cognitive performance improves as birth weight increases, leads to the question of whether this may also be the case for the relationship between intelligence and birth weight in the normal range. If birth weight is an important factor in the etiology of intelligence among the normal birth weight population, this may help to untangle some of the influences on the development of intelligence. Furthermore, if birth weight is identified as a possible target for intervention, increasing birth weights might have a beneficial impact on intelligence at a population level. To use the physiological analogy of blood pressure, small changes in absolute blood pressure in individuals have a significant impact on the distribution of blood pressure in the population and hence affect the prevalence of hypertension-associated diseases. For example, decreasing individual blood pressure levels by 5%, if achieved within the majority of the population, might produce a 30% reduction in strokes (Rose, 1992). Thus, apparently trivial changes among individuals could have massive public health and economic implications.

In this article, we describe a systematic review of the literature that focused on the following research question: What is the relationship between birth weight and childhood intelligence differences in term (37–42-week gestation) deliveries of normal birth weight infants (more than 2,500 g)? A systematic review was required because reviews of literature not involving predefined criteria may be biased (Cochrane Non-Randomised Studies Methods Group, 2004), and the present area of research is one in which there have been strongly held views and assertions. For example, "there is no known direct relationship between birth weight and later psychological performance" (Klein, Lester, Yarborough, & Habicht, 1972, p. 251), and "within the range of full-term birth weights . . . few investigators have found differential effects of birth weight on later intelligence" (Scarr, 1969, p. 249). In neither case did these authors cite references to support their position. More recently, the converse has been stated, that "there is now a consensus that the cognitive effects of birth weight can be observed across its full range in the normal population, at least in the West" (Richards, Hardy, Kuh, & Wadsworth, 2003, p. 7A). The present review is intended to be informative for both specialist and general audiences because, although birth weight and childhood intelligence may seem to be the specific province of developmental and cognitive psychologists, neonatologists, and educationalists, early life influences on later abilities are of interest to a wide range of other psychologists, researchers, practitioners, policymakers, and the general public.

Objectives

The primary objective of this systematic review was to establish whether published and unpublished data show any evidence of a

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relationship between birth weight in the normal range and measured intelligence differences in childhood. Therefore, we critically evaluated the relevant studies with a view to integrating the past literature—if possible—to formulate a general statement (Cooper, 2003). We also sought to identify questions that will stimulate future endeavors in the field of early life influences on human intelligence differences.

Methods of Data Collection

The guidelines published by the Cochrane Collaboration (Cochrane Non-Randomised Studies Methods Group, 2004) and the Meta-Analysis of Observational Studies in Epidemiology Group (Stroup et al., 2000) were followed in the design, performance, and reporting of this systematic review. The recent editorial on literature reviews published in *Psychological Bulletin* (Cooper, 2003) also provided guidelines for taxonomy and reporting.

Types of Studies

Studies were considered for inclusion if they provided quantitative data on the association between birth weight and cognition relevant to the entire range of birth weights. All observational studies (cohort and case-control studies) were considered for inclusion. In case-control studies (normally involving outcomes for low birth weight babies), controls who had birth weights in the normal range were eligible for inclusion if (a) they were representative of the underlying population (i.e., not matched to case participants apart from setting) and (b) a birth weight–cognitive ability association (not simply a mean and standard deviation) was reported. Birth weight had to be measured, not recalled (Andersson et al., 2000), and intelligence differences had to be assessed by means of a psychometric test rather than educational achievement, behavioral outcomes, or psychomotor skills.

Types of Participants

Participants in the included studies were those with birth weights throughout the normal range who completed valid psychometric cognitive tests after their 5th birthday and before their 17th birthday.

Data Evaluation

Search Strategy

We searched the databases MEDLINE (1966–April 2003), PsycINFO (1974–June 2003), EMBASE (1980–June 2003), and ERIC (1965–April 2003) using the search strategies listed in the Appendix. We excluded duplicates from subsequent searches. In brief, we looked for articles whose main focus was birth weight but also mentioned cognition (or any of its synonyms) or cognitive tests (or synonyms) or whose main focus was cognition (or any of its synonyms) or cognitive tests (or synonyms) but also mentioned birth weight. Articles with *low* in the title were separated (although these articles were also considered in the initial searches in case the control group provided the relevant information). This search strategy was designed to have high sensitivity, but as a consequence, it was low in specificity. We anticipated that a large number of irrelevant articles would be included, but this was necessary owing to the lack of a specific search term to identify relevant studies. We performed a manual search of the reference lists of all primary articles retrieved, and we searched for articles citing primary articles in the Science Citation Index.

We attempted to include unpublished studies by searching the resources suggested by the Centre for Reviews and Dissemination (2001) and the Cochrane Non-Randomised Studies Methods Group (2004).

1. We searched for reports, discussion papers, and so forth in (a) the System for Information on Grey Literature (http://arc.uk.ovid.com/webspirs/login.ws), (b) the National Technical Information Service (http://www.ntis.gov/search/), and (c) the British Library Public Catalogue (http://blpc.bl.uk/).

2. We searched for dissertations and theses in (a) the Cumulative Index to Nursing and Allied Health (http://www.cinahl.com/) and (b) ProQuest Digital Dissertations (http://wwwlib.umi.com/dissertations/gateway).

3. We searched all of the birth cohorts included in the National Research Register (http://www.update-software.com/national/) and checked for eligible studies.

4. We searched for conference proceedings in (a) ISI Proceedings (http://portalt.wok.mimas.ac.uk/portal.cgi?DestApp=ISIP&Func=Frame) and (b) zetoc (http://zetoc.mimas.ac.uk/zetoc/).

Also, we contacted the authors of each of the primary studies included in the review to ask whether they were aware of any additional studies (including unpublished analyses). Details on the search strategies used for each database are available from the authors.

Exclusions

Studies were excluded if the groups assessed were not representative of the general population, that is, samples that were (a) matched controls of low birth weight or premature infants, (b) from high-risk or atypical populations (e.g., populations exposed to famine or high lead concentrations), (c) part of intervention studies (e.g., breast feeding), or (d) primarily composed of multiple births (e.g., twins). No language restrictions were imposed in the searching of databases so as to ascertain whether suitable studies may have been published in other languages (no such studies were found). If multiple studies were published on the same cohort at different ages, only the most recent eligible published report was included. Studies were excluded if no data were presented concerning the association between birth weight and intelligence test scores. As a means of maximizing possible inclusions, no restrictions were specified a priori in terms of study quality, but quality was stringently assessed.

Study Selection

The database searches produced 3,207 article titles: 1,927 from MEDLINE, 527 from PsycINFO, 422 from ERIC, and 331 from EMBASE. Of these articles, 91 were retrieved, and 7 met our selection criteria (see Figure 1). The extended searches identified one study in a book chapter and one eligible study reported in the proceedings of a conference. The latter study has not yet been published, but the authors made the data from their draft paper available. Two relevant PhD theses were identified, although they did not meet our selection criteria. Three articles were found in which the participants were more than 17 years of age.

A high proportion of the 3,207 publications were rejected at the first stage of reading the title. Our very inclusive search strategy meant that many studies were identified that were clearly not eligible for this review, such as those focusing on predictors of low birth weight, relationships between birth weight and morbidity or mortality, social influences on education, and interventions involving mothers or babies. In instances in which there was any possibility that the report contained data relevant to the aims of the review, the abstract was read to clarify eligibility. Articles were retrieved when the decision could not be made solely on the basis of the title or abstract. Among the 91 articles retrieved, the majority of those excluded were (a) case-control studies of low birth weight babies in which no data on birth weight–IQ associations were included for the control group, (b) studies of multiple births, or (c) studies drawn from selected populations (see Figure 1).

Selection criteria were applied independently by Susan D. Shenkin, but agreement regarding articles to include was reached by consensus. John M. Starr and Ian J. Deary checked a random sample of references to ensure that no relevant articles were missed, and Susan D. Shenkin and John M. Starr examined a random sample of articles to ensure that agreement was reached in regard to exclusions. No new studies were identified for inclusion. Data from each included study were extracted onto paper forms based on the Scottish Intercollegiate Guidelines Network (2004) guidelines for interpreting cohort studies. Data extracted included details on the source population, proportion of participants included in analyses, loss to follow-up, validation and blindness of outcome measures, and the extent to which confounding was considered. This information was recorded in an open-ended fashion.

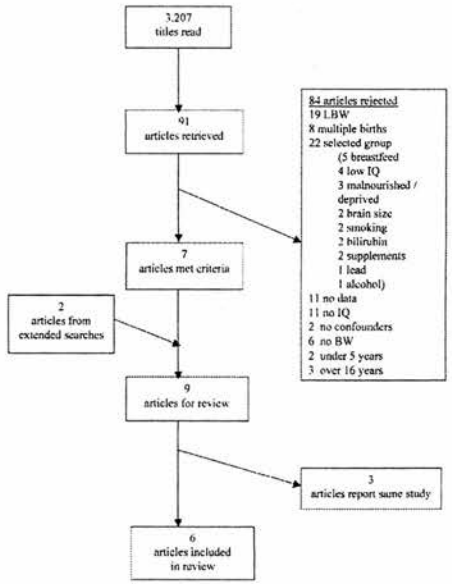


Figure 1. Flowchart of selection of eligible studies. LBW = low birth weight; BW = birth weight.

Of the nine reports eligible (seven journal articles, one unpublished paper, and one book chapter), three contained results similar to those included in another report. First, in regard to the 1946 British birth cohort (Richards, Hardy, Kuh, & Wadsworth, 2001, 2002) data were used from the more recent study. Second, in the case of the 1950–1954 Birmingham study (McKeown, 1970; Record, McKeown, & Edwards, 1969), data were used from the substantive article (Record et al., 1969) rather than the lecture report (McKeown, 1970) because they were presented in a form that made them easier to compare with other studies. Third, in terms of the 1958 British birth cohort (National Child Development Study; Goldstein & Peckham, 1976; Jefferis, Power, & Hertzman, 2002), data are presented from the article including social information (Jefferis et al., 2002), again because these data were presented in a form that made them easier to compare with other studies. The original report presented the results for reading scores at age 11 as fitted constants and an analysis of variance table, and the pattern of results was broadly similar (Goldstein & Peckham, 1976). Thus, six studies were included in the final review (see Table 1), and they are described here in chronological order.

Methods of Review

Descriptive summary statistics regarding cognitive test scores for birth weight categories (as reported in the studies) are presented in Table 2 and displayed graphically in Figure 2. If reported in the study, the simple correlation between birth weight and cognitive test scores is included, as is the correlation corrected for confounders (see Table 2 and Figure 3).

When we designed the review, we hoped that the correlation between birth weight and intelligence would be reported as a single statistic and that the studies would be sufficiently similar to allow these correlations to be combined in a numerical summary, weighted according to size and quality of study (i.e., a formal meta-analysis). However, the studies were all markedly different in terms of initiation date, age of participants, tests used, and outcome measures (as described subsequently), and it was our conclusion that a numerical summation of their results would be unjustifiable and invalid. In any event, few of the studies contained a single correlation statistic or the data from which this statistic could be calculated. A more valid method for such a diversity of studies is a narrative review of each study, followed by an attempt to form unbiased conclusions. This methodology still falls under the umbrella of systematic review, given that the literature is searched systematically and the data extracted in a predetermined way.

Table 1
Characteristics of Studies Included in Review

Study	Source population	Birth			Cognitive test					
		Year(s)	*n*[a]	% male	Year(s)	*n*[a]	% male	Age (years)	Test	Validation
Record et al. (1969): retrospective matching of data	All births in Birmingham, England	January 1950–September 1954	86,630	NR	NR; probably 1961–1965	(50,172) 41,534 singletons matched to birth data	NR	NR (around 11 years)	Verbal reasoning from 11+ exam (standard school test)	NR
Matte et al. (2001): prospective data collection	National Collaborative Perinatal Project; 12 medical centers in U.S.; singleton sibling randomly from sibship sample	1959–1966	1,683 (selected from 3,484 siblings and about 58,000 pregnancies)	48.2	1966–1973	1,683	48.2	7	Verbal and performance (WISC)	NR
Shenkin et al. (2001): retrospective matching of data	Live singleton births from one hospital, Edinburgh, Scotland	1921	985	NR	1932	(87,498) 449 matched on birth weight	54.8	11	"Closely related to Moray House Test No. 12"	1,000 Retested on Stanford revision of Binet–Simon
Richards et al. (2002): prospective data collection	National survey of health and development; singleton births, Britain	March 1946	3,900 complete data (5,362)	NR	1954 (1961, 1972, 1989)	2,758	NR	8 (15, 26, 48)	Reading comprehension, word pronounciation, vocabulary, nonverbal reasoning	Referenced
Jefferis et al. (2002): prospective data collection	1958 British birth cohort (National Child Development Study); singletons	March 1958	11,137 married mothers (13,980)	NR	1965 (1979, 1984, 1991)	10,845 (but discrepant with other *ns*; i.e., 6,216 males + 5,908 females = 12,124)	51.3	7 (11,16, qualifications at 33)	Math test (also reading, draw a man, copy design; NR)	NR
Corbett et al. (2004): prospective data collection	All births in Newcastle, England	April 1987–March 1988	3,655	NR	1997(?)–1998	2,030 (2,294)	NR	10	Picture vocabulary; problems of position, math, reading	Referenced

Note. NR = not reported; WISC = Wechsler Intelligence Scale for Children.
[a] Items in parentheses are total numbers from which study was drawn or data not directly relevant to the review (see text).

Table 2
Relationship Between Birth Weight and Cognitive Ability: Results From Studies Included in Review

Study	Correlation uncorrected	Correlation corrected for confounders	Confounders considered	IQ test blind to BW?	Notes	Categorical data uncorrected			
							Test score		
						BW (kg)	*M*	*SD*	*n*
Record et al. (1969)	NR; data divided into GA categories; these data for 40/40 weeks only	Block diagram standardized for sex and BR; data also reported for firstborns only	Sex GA BR	Yes (NR)		2.0–2.49 2.5–2.99 3.0–3.49 3.5–3.99 4.0–4.49 4.5+	94.5 97.9 100.1 102.1 102.8 103.2	NR	454 3,576 9,062 7,102 1,904 336
Matte et al. (2001); from sibship sample	One-sibling sample linear regression, IQ difference per 100 g BW: boys .77, girls .63	One-sibling sample linear regression, IQ difference per 100 g BW: boys .46 (95% CI = .25, .66), girls .28 (95% CI = .09, .47)	Sex GA > 37/40 weeks BR MA PE (maternal) Race (White vs. other)	NR	From one-sibling sample, estimated average IQ difference: kg boys girls 1.5–2.49 −6.6 −5.7 2.5–2.41 −4.9 −3.6 3.0–3.99 1.0 1.0 3.5–3.99 3.6 4.2	1.5–2.49 2.5–2.99 3.0–3.44 3.5–3.99	91.9 94.5 97.7 100.7		187 892 1,578 827
Shenkin et al. (2001)	$r = .17$	Total $r = .25$, $p < .001$; boys $r = .23$, $p < .003$; girls $r = .27$, $p < .002$	GA MA BR SC (husband's occupation) Legitimacy	Yes (NR)	BW $\beta = .20$ (3.8% of variance)	<2.5 2.5–3.0 3.01–3.5 3.51–4.0 4.01–4.5 >4.5	30.6 34.4 37.3 37.8 44.7 35.1 (out of 76)	NR 19.4 15.0 14.6 14.7 10.6 9.4	25 102 164 115 34 9
Richards et al. (2002)	$p < .001$	kg *z* 95% CI −2.5 −.22 −.39, .06 −3.0 −.02 −.12, .08 −3.5 Reference −4.0 .17 .09, .25 −5.0 .17 .06, .29 $p < .001$	Sex BR MA SC (father's occupation) PE (maternal) Postnatal height and weight	NR	Followed longitudinally to adulthood	BW (kg)	*z*	95% CI	
						1.5–2.5	−.27	−.47, −.09	
						2.51–3.0	−.06	−.17, .04	
						3.01–3.5	Reference	Reference	
						3.51–4.0	.04	−.08, .17	
						4.01–5.0	.04	−.08, .17	
Jefferis et al. (2002)	Male $R^2 = .8$; female $R^2 = 1.0$ Male $\beta = .17$ (95% CI = .12, .22); female $\beta = .19$ (95% CI = .14, .25)	Male $\beta = .15$ (95% CI = .10, .21); female $\beta = .19$ (95% CI = .14, .25)	GA SC (father's occupation) MA PE BR Breast feeding	NR		Male			
						<2.5	−.13	−.27, .01	
						2.5–3.0	−.08	−.08, −.01	
						3.01–3.5	.07	.03, .18	
						3.51–4.0	.14	.10, .18	
						>4.0	.17	.10, .24	
						Female			
						<2.5	−.33	−.44, −.22	
						2.5–3.0	−.12	−.17, .06	
						3.01–3.5	−.01	−.05, .03	
						3.51–4.0	.08	.03, .13	
						>4.0	.12	.03, .21	

Table 2 (*continued*)

Study	Correlation uncorrected	Correlation corrected for confounders	Confounders considered	IQ test blind to BW?	Notes	Categorical data uncorrected				
						BW (kg)	Test score			
							β	*M*	*SD*	95% CI	*n*
Corbett et al. (2004)	$r = .103$; $p < .01$	NR Multiple linear regression with deprivation: GA R^2 change = .008, $p < .002$	Sex GA Deprivation Weight in infancy	Yes		−1 to −0.5	0.14			−1.4, 1.6	
						−0.5 to 0	0.80			−0.6, 2.2	
						0 to 0.5	1.52			−0.3, 3.1	
						0.5 to 1	2.54			0.8, 4.3	
						>1	0.96			−0.9, 2.8	

Note. BW = birth weight; NR = not reported (following "Yes" in the "IQ test blind to BW?" column, NR refers to instances in which blindness to BW can be assumed on the basis of the study's design, although it was not explicitly reported); GA = gestational age, BR = birth rank; MA = maternal age; PE = parental education; SC = social class; CI = confidence interval.

The data did not permit the construction of a funnel plot (Egger, Davey, Schneider, & Minder, 1997) to illustrate formally the possibility of publication bias. However, with such a small number of published studies, all of which showed a positive relationship (as described subsequently), the possibility of publication bias cannot be discounted.

Assessment of Confounding Factors

Many variables were described in the studies as potential confounders of the birth weight–IQ association. Potential confounders are those factors that are independently related to both birth weight and intelligence but are not part of the causal chain (Hennekens & Buring, 1987; Woodward, 1999). The term *confounder* is often used imprecisely in epidemiology or medical journals to refer to any variable included in the analyses that is not the primary independent or dependent variable of interest. Psychologists tend to use the term *covariate* in this situation, and they are more specific in their use of "mediators" when a covariate might be implicated causally between the independent and dependent variables. Here we use the term *confounder* to apply to variables that were used to examine whether their inclusion adjusted the birth weight–IQ association. In using this term, we are following the conventions of the original authors, and it should not be taken to imply our acceptance of a particular causal interpretation.

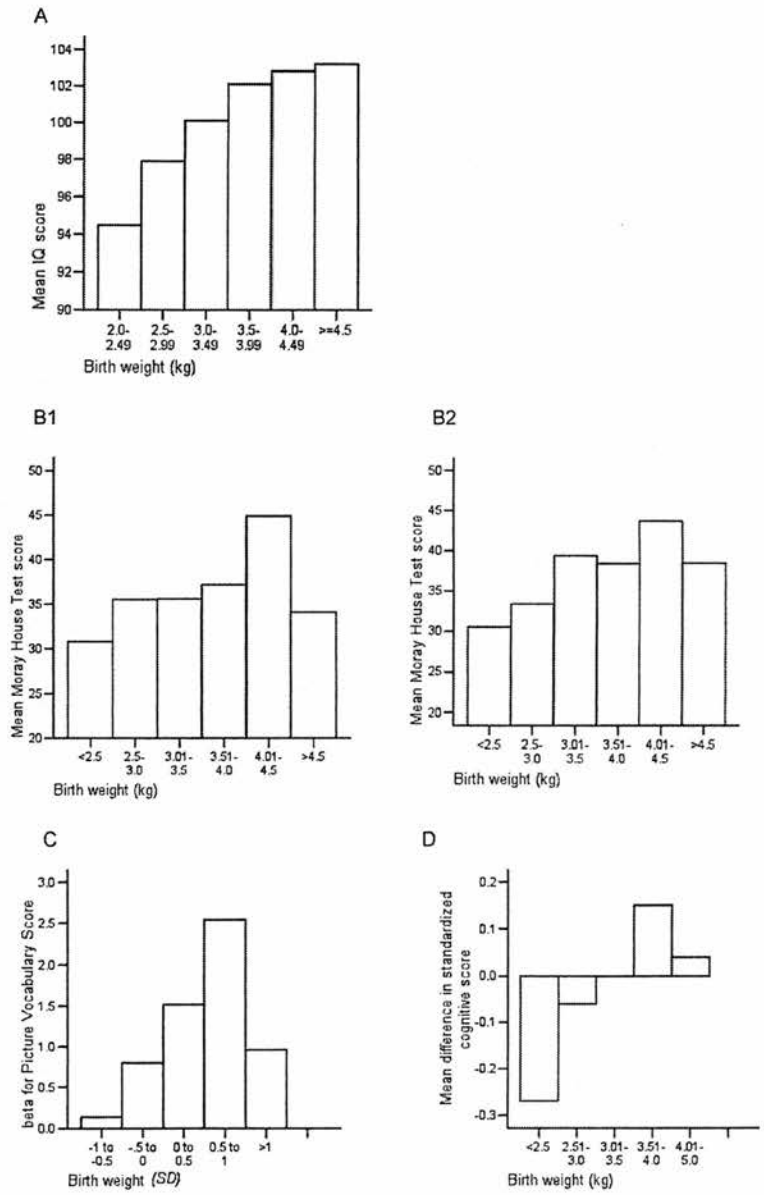
Analysis and Interpretation

The studies eligible for inclusion in this review varied markedly, despite the strict application of clear inclusion criteria: The cohorts studied were born over more than half a century (from 1921 to 1987) on two different continents (North America and Europe), they differed markedly in size (from 449 to 41,534), and data were collected in several ways (prospectively as well as retrospectively; see Table 1). Therefore, we evaluate the studies individually, in historical order. Studies that did not meet the inclusion criteria but add useful information are also discussed, as are three studies of the association between birth weight and intelligence in adults (i.e., those more than 17 years of age; see Tables 3 and 4 and Figure 4).

Birmingham Births: 1950–1954

The oldest study (Record et al., 1969) was also the largest. Among 86,630 births occurring in Birmingham, England, from 1950–1954, 50,172 (57.9%) were matched to verbal reasoning test scores from the 11+ examination, which was used to guide placement of children aged about 11 years from primary into secondary education. Of these scores, 41,534 (82.8%) were matched to a valid hospital or domiciliary birth weight and gestational age. Validation of the verbal reasoning test was not described, although it has been reported to be age adjusted and to have a mean of 100 and standard deviation of 15 for children born in each month. It was not explicitly stated that the test was performed blind to birth weight; however, we assumed this to be the case, because the data were collected retrospectively, with the test being conducted routinely at school. The proportion of participants of each sex was not reported, although many of the results were divided by sex.

The authors explicitly considered confounding by sex, birth



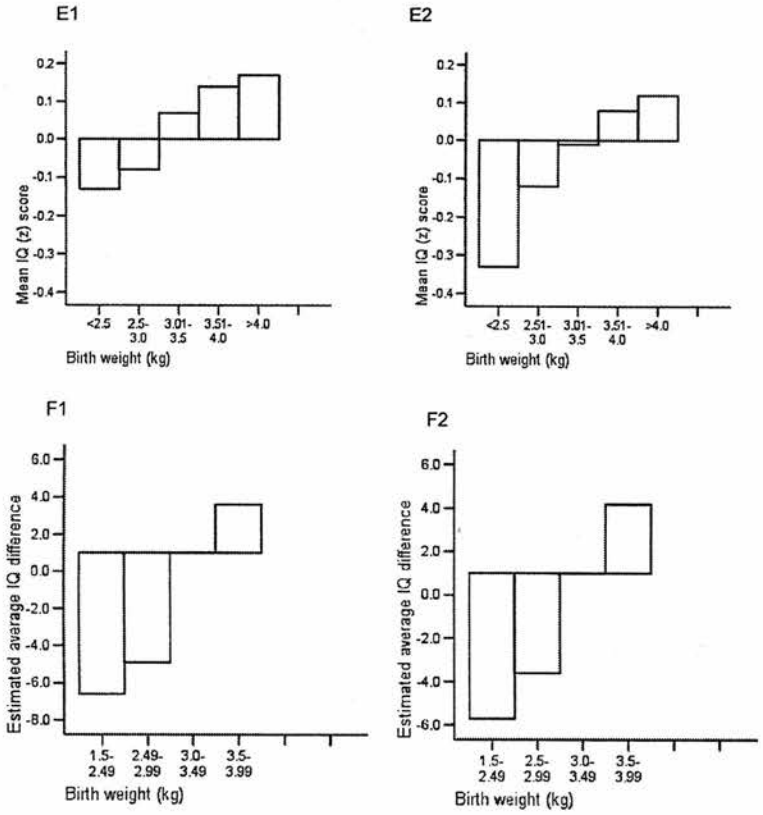


Figure 2. Birth weights and mean cognitive test scores in childhood, not corrected for confounders. A: Record et al. (1969; United Kingdom [UK]; N = 41,534). B1: Shenkin et al. (2001; UK; male n = 246). B2: Shenkin et al. (2001; UK; female n = 203). C: Corbett et al. (2004; UK; N = 2,030). D: Richards et al. (2002; UK; N = 2,758). E1: Jefferis et al. (2002; UK; male n = 6,216). E2: Jefferis et al. (2002; UK; female n = 5,908). F1: Matte et al. (2001; United States; one-sibling sample; male n = 811). F2: Matte et al. (2001; United States; one-sibling sample; female n = 872.

rank, and gestational age but explored these relationships using a "three dimensional histogram . . . built with Lego and photographed" (Edwards, 2001, para. 5), rather than multiple regression. This was explained in a recent letter to be "in view of substantial birth-rank effects" (Edwards, 2001, para. 5), although other researchers believe that multiple regression would be a suitable method for analysis if the appropriate interactions are considered (Richards, 2001). The histogram showed mean verbal reasoning scores (standardized for sex and birth rank) according to birth weight and duration of gestation. There was an increase in verbal reasoning score for each birth weight category, with a larger effect at smaller birth weights (see Table 2 and Figure 2). Mean IQ increased from 94.5 points for the smallest birth weights (2,000–2,500 g) to 103.2 points for the largest weights (more than 4,500 g). Mean IQ differences were 3.4 points between the lowest two categories and 0.4 points between the highest two. Standard deviations were not reported. The data presented in Table 2 and Figure 2 apply only to 22,457 births with gestation periods of 40–42 weeks, but the three-dimensional histogram in the original article shows a similar pattern for all gestational ages. Information on social class (based on father's occupation) was collected (Record et al., 1969) but not included in the analyses comparing

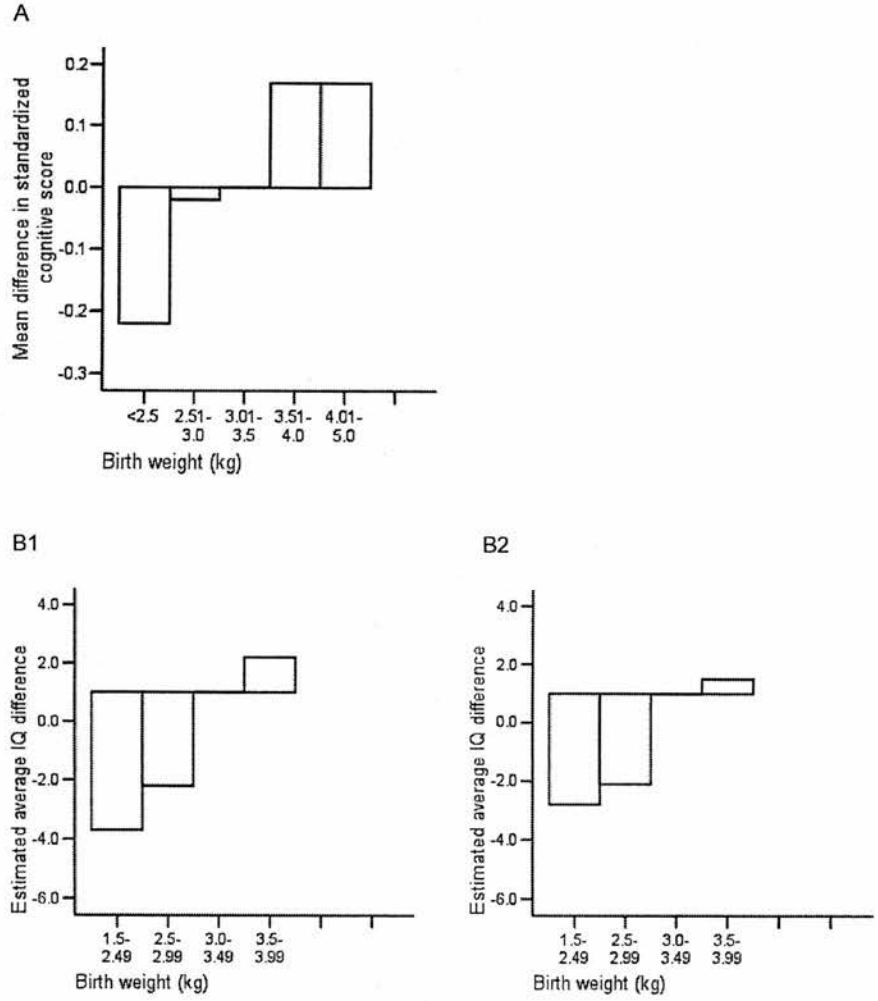


Figure 3. Birth weights and mean cognitive test scores in childhood, corrected for confounders, where results were available. A: Richards et al. (2002; N = 2,758), adjusted for sex, birth order, social class, mother's education, and mother's age. B1: Matte et al. (2001; one-sibling sample; male n = 811), adjusted for race, mother's education, mother's age, family socioeconomic index, and birth order. B2: Matte et al. (2001; one-sibling sample; female n = 869), adjusted for race, mother's education, mother's age, family socioeconomic index, and birth order.

Table 3
Characteristics of Studies Not Included in Review, Age at Testing Above 17 Years

Study	Source population	Birth			Cognitive test					
		Year(s)	*N*	% male	Year(s)	*N*	% male	Age (years)	Test	Validation
Seidman et al. (1992): retrospective matching of data	Maternity ward births in West Jerusalem, at Israel Defence Forces Draft Board	1964–1970	NR ("<2% excluded")	NR	NR (probably 1981–1987)	20,567	100	17	Translated version of verbal Otis test and nonverbal matrices	"Transformed into values that correlate with WAIS"
Sorensen et al. (1997): retrospective matching of data	Births in Denmark, registered with draft board	January 1973–?	NR Birth weight measured in 250-g categories	NR	1993–1994	4,300 (matched to birth data)	100	"About 18"	Boerge Prien test	Correlated .82 with full-scale IQ on WAIS
Martyn et al. (1996): retrospective matching of birth data and cross-sectional data collection	Singletons born in two hospitals in Preston and Sheffield, England, and still living in area	1920–1943	NR	NR	NR	1,576	NR	Mean of 60.9 years (*SD* = 2.1; differed by area)	Alice Heim 4; Mill Hill	NR

Note. NR = not reported; WAIS = Wechsler Adult Intelligence Scale.

birth weight and verbal reasoning score. Multiple births were excluded.

A major strength of this study was its selection of a large sample from the general population of both hospital and home births. However, no attempt was made to describe the representativeness of those included, and thus we cannot determine the extent of selection bias. The association between birth weight and verbal reasoning was described and illustrated clearly, but no single correlation was presented (although, because of the nonlinear shape of the association, this may well not have been appropriate). The other major limitation was the lack of consideration of confounders in the unitary analysis, although many of the relevant confounders were measured in the study. It remains possible that the associations observed were the result of residual confounding; that is, they were not direct causal associations between birth weight and cognitive ability but were due to factors related to both birth weight and cognitive ability (confounding variables) that were not included in the analysis. The next four studies to be described were all published in 2001 and 2002, illustrating the resurgence of interest in the relationship between birth weight and cognitive ability.

National Collaborative Perinatal Project

Matte, Bresnahan, Begg, and Susser (2001) used data derived from the National Collaborative Perinatal Project conducted in the United States, in which approximately 58,000 pregnancies involving about 40,000 women between 1959 and 1966 were followed prospectively. This study's main purpose was to examine the relationship between birth weight and intelligence in siblings and control for family environment (as discussed further subsequently); however, the study included a one-sibling sample of 1,683 (2.9% of total births) in which one child was randomly selected from each family. All of these children were singletons with gestational ages of 37 weeks or more and birth orders below five. The sibship sample included those children with at least two siblings of the same sex. This sample was relatively affluent and more likely to include White and younger mothers than the National Collaborative Perinatal Project as a whole.

The IQ test used was part of the WISC, a well-recognized and widely validated intelligence test, although its formal validation was not reported in the study. Whether the tests were done blind to birth weight was not reported. Unadjusted analyses showed that IQ increased from 91.9 points among those in the smallest birth weight category (1,500–2,500 g) to 100.7 among those in the largest category (3,000–4,500 g); the test score difference between the smallest two groups was 2.6 points, and the difference between the heaviest two groups was 3.0 points. However, the upper limit of birth weight was 4,000 g (see Table 2). Confounders included in the analysis were socioeconomic index (a scale reflecting household income and education and occupation of head of household), sex, birth order, maternal age, education, and race. Adjusting for confounders in the linear regression decreased the strength of the relationship between birth weight and IQ but did not eliminate it, and it remained statistically significant. This could mean that there was a true positive relationship or that this relationship was still due to residual confounding. The association was stronger for boys than girls: A 1,000-g increase in birth weight was related to a

Table 4
Relationship Between Birth Weight and Cognitive Ability: Age at Testing Above 17 Years

Study	Categorical data uncorrected				Correlation uncorrected	Correlation corrected for confounders			Confounders considered	IQ test blind to BW?	Notes
	BW (kg)	Test score *M*	Test score *SD*	*n*		*β*	*SE*	*p*			
Seidman et al. (1992)	<2.0	98.3	14.9	224	NR	−6.5	1.1	<.0001	BR	Yes (NR)	Bar chart showed IQ scores of low BW vs. normal BW distribution shifted to left Confounders explained 22% of variance
	2.0–2.4	100.1	15.9	704		−3.6	0.6	<.0001	MA		
	2.5–2.9	102.1	17.3	3,342		−1.6	0.3	<.0001	Ethnic origin (paternal)		
	3.0–3.4	102.8	18.5	8,555		Reference			SC (residence and tax level)		
	3.5–7.9	103.0	15.3	5,896		0.4	0.3	.16			
	4.0–4.4	101.7	16.0	1,595		−0.2	0.4	.72	PE		
	4.5+	100.8	15.8	251		0.9	1.0	.37			
Sorensen et al. (1997)	<2.5	39.9	9.3	171	NR	Graph of quadratic spline regression: nonlinear relationship			GA	Yes (NR)	
	2.6–3.5	42.2	9.3	603					BR		
	3.1–3.5	42.6	9.7	1,451					MA		
	3.6–4.0	43.5	9.4	1,453					Marital status		
	4.1–4.5	44.6	9.6	515					Employment		
	>4.5	44.6	9.5	105					Birth length		
Martyn et al. (1996)	<2.5	20.8	NR	74	NR	NR (p = .17)			Age	NR	Also assessed decline in cognitive function (p = .42)
	2.5–2.9	21.8	NR	266					SC		
	3.0–3.4	22.6	NR	543					Individual data set		
	>3.4	23.0	NR	693							

Note. BW = birth weight; NR = not reported; (following "Yes" in the "IQ test blind to BW?" column, NR refers to instances in which blindness can be assumed on the basis of the study's design, although it was not explicitly reported); BR = birth rank; MA = maternal age; SC = social class; PE = parental education; GA = gestational age.

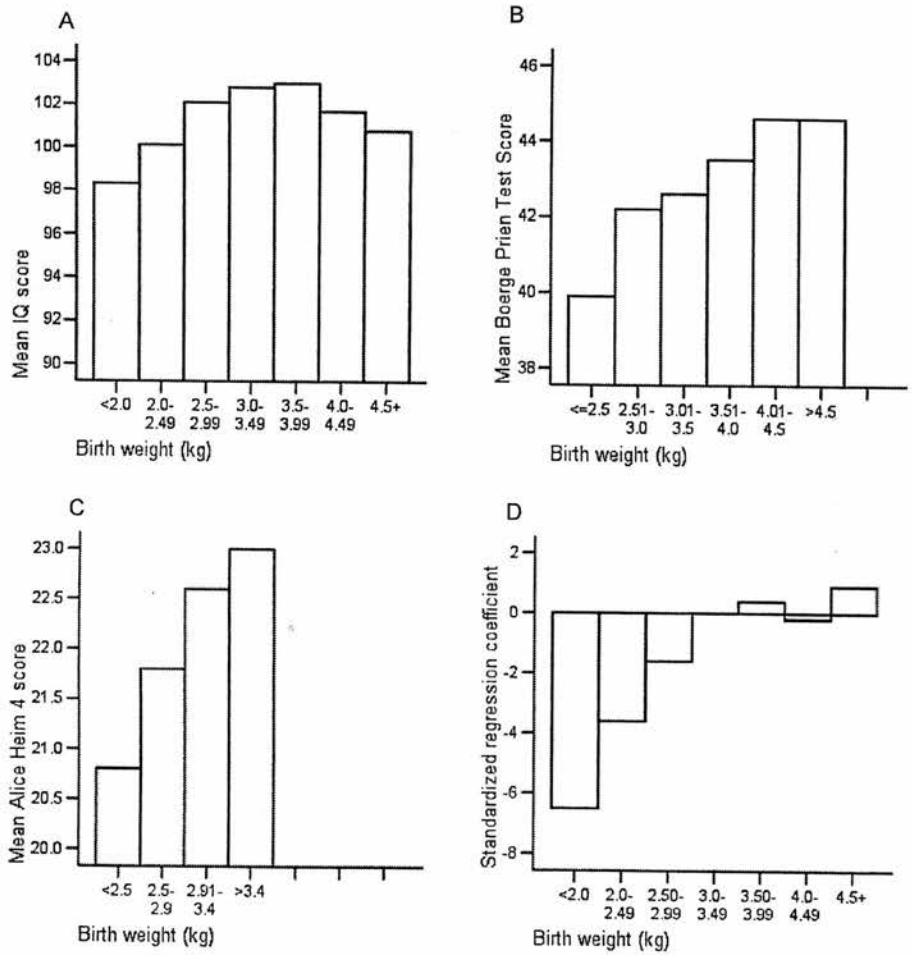


Figure 4. Birth weights and mean cognitive test scores in adulthood. A: Seidman et al. (1992; Israel; N = 20,567). B: Sorensen et al. (1997; Denmark; N = 4,300). C: Martyn et al. (1996; United Kingdom; N = 1,576). D: Seidman et al. (1992), corrected for ethnic origin, birth order, maternal age, parental education, and social class.

7.7-point IQ increase among boys (4.6 points when adjusted for confounders, 95% CI = 0.25, 0.66) and to a 6.3-point among girls (2.8 points after adjustment, 95% CI = 0.09, 0.47).

This study reported the association of IQ with birth weight in both a continuous and a categorical form. Birth weights of 1,500 to 3,999 g were included, and thus there was the possibility of the positive association being due to very small births. Mean IQ did, however, increase in roughly even increments across the birth weight categories (see Figure 2). Some of the analyses were repeated for birth weights above 2,500 g, and results were "essentially identical" (Matte et al., 2001, p. 312) to those observed for the overall sample; however, this information was not reported for

the one-sibling sample. The restriction of the upper weight limit (4,000 g) seems arbitrary, and the authors did not explain whether this restriction was imposed before or after the data analysis. Overall, however, this study was well designed, and it attempted to minimize bias and control for confounding to the extent possible. We discuss in more detail later the use of siblings to control for family environment, but, in brief, IQ differences among same-sex siblings were still significantly related to birth weight in the case of boys, implying that the birth weight–IQ association cannot be explained by family social environments.

Scottish Mental Survey

The smallest study (N = 449; Shenkin et al., 2001) involved the use of the oldest records, including 45.6% of eligible births occurring at a single hospital in 1921. Mean birth weights among those traced and those not traced were not significantly different, but the former were more likely to be male, to be legitimate, to have older mothers, and to be later in the birth order. The sample was therefore biased with respect to the remainder of the hospital births and also likely to be different from the overall population; indeed, the sample's mean cognitive test score was higher than that of the general population, although the effect size was small. The test used—a version of Moray House Test No. 12 (Scottish Council for Research in Education, 1933)—was concurrently validated against the Stanford-Binet Intelligence Scale ($r \approx .8$) and conducted at school blind to birth weight. Results were reported as raw test scores and not converted to standardized units. Confounders considered were sex, social class (husband's occupation at the time of the birth), legitimacy, gestational age, maternal age, parity, and exact age at cognitive testing. Parent IQ, postnatal factors, and other social influences were not included.

There was a significant relationship between birth weight and test score among both boys and girls (overall r = .17, $p < .001$), and this association increased when correcting for confounders (r = .25, $p < .001$). Reasons for this finding, which contradicted the results of other studies showing that the relationship is weakened when corrected for confounders, were not discussed. This study also showed a decrease in IQ scores at the highest birth weights; however, there were only a few such cases, and excluding them from analyses did not affect the results. The portion of the variance in IQ explained by birth weight (3.8%) was less than that explained by social class (6.6%). As well as correcting for confounders in multivariate analyses, the authors used structural equation modeling to test whether the association between birth weight and IQ was in fact due to birth weight mediating the effect of parental social class. The model with the best fit indicated that social class, birth weight, and age at testing had independent influences on test score. This introduced some new methodology to the area but should be treated with caution in view of the relatively small, and biased, sample. Also, because of the huge changes in social structure and medical care in the past 80 years, these results may not be directly applicable today, although consistent results across time would reinforce the birth weight–IQ hypothesis.

British 1946 Birth Cohort

A prospective study of all single, legitimate births occurring in England, Scotland, and Wales during 1 week in 1946 (Richards et al., 2002) also revealed a positive relationship between birth weight and cognitive ability in childhood. The cohort was most recently tested at 43 years of age, and the adult findings are discussed later. Of the 5,362 members of the original birth cohort, 762 had not undergone cognitive testing at 8 years of age. Of the 4,600 cohort members with at least one cognitive test score available, 3,900 (85%) had complete information (including confounders). Those with missing information had lower mean cognitive scores at 8 years of age, and in later years they were more likely to be unmarried, less literate, in the manual social class group, and mentally ill than the general population. Whether those with and without complete data differed in terms of birth weight was not reported. At age 8, 2,758 of the 3,900 cohort members just mentioned (70.7%) had complete data.

Cognitive test scores did increase with birth weight (see Table 2 and Figure 2); in comparison with the reference group (3,500–4,000 g), z scores were −.27 (95% CI = −.47, −.09) for those with birth weights of 2,500 g or less and .04 (95% CI = −.08, .17) for those with birth weights between 4,000 and 5,000 g. There also seemed to be a decrease in cognitive test scores at the highest birth weights (4,000–5,000 g), but this disappeared when corrected for confounders (see Figure 3), and it was reported to be due to those later in the birth order who were heavier but performed less well on IQ tests. Various cognitive measures were used, and these measures differed at each testing wave. At the age 8 measurement, tests of reading comprehension, word pronunciation, vocabulary, and nonverbal reasoning were used. Validation of the cognitive tests used was not reported, although a reference was provided in which the tests are described in detail. Confounders considered were sex, father's social class (based on occupation, although the exact method of classification was not reported), mother's education and age, birth order, and postnatal height and weight. Of major importance, however, this study did not include gestational age, limiting interpretation of birth weight as an indicator of fetal growth. The survey also included an assessment at age 15, but we do not report these results here because they exhibited a pattern broadly similar to that at age 8. This study included data on postnatal growth as well, and the authors concluded that growth (particularly between the ages of 2 and 4 years) was independently associated with cognitive development.

1958 British Birth Cohort Study

Another large prospective British birth cohort study (Jefferis et al., 2002) followed singletons with gestational ages of 32 to 44 weeks who were born legitimately in 1 week during March 1958. Of eligible children, 77.6% (n = 10,845) participated at the age of 7 years (although the numbers provided in the text and tables did not always tally). These participating children had birth weights similar to those of the nonparticipants; lower proportions were from social class IV or V or single households. Participants underwent "age appropriate tests at school" (Jefferis et al., 2002, p. 306). The math test exhibited the best discrimination of ability at different ages (too many children had high scores on the reading test), and thus these results were reported in the most detail. Highest qualifications reached at the age of 33 years were also reported. Once again, validation of the tests was not described, although relevant references were cited; in addition, it was not explicitly stated that testing was blind to birth weight, although this

was almost certainly the case. Confounders considered in the analysis were gestational age, social class (father's occupation), maternal age, breast feeding, parental education, and parity.

This study also showed an increase in math test score with increasing birth weight among both sexes (see Table 2 and Figure 2). For example, among boys, z scores increased from −.13 (95% CI = −.27, .01) for the smallest birth weight category (less than 2,500 g) to .17 (95% CI = .10, .24) for the largest category (more than 4,000 g), and the same pattern was shown for the other tests (reading, draw a man, copying designs, verbal and nonverbal ability, and even adult qualifications). The pattern was similar at ages 7, 11, and 16 and when preterm and disabled children were excluded. Adjustment for confounders weakened the relationship slightly: For each 1,000-g increase in birth weight, math score beta coefficients increased by .17 (95% CI = .12, .22) among boys and by .19 (95% CI = .14, .25) among girls; after adjustment, the corresponding increases were .15 (95% CI = .10, .21) and .19 (95% CI = .14, .25; see Table 2). Although birth weight was significantly related to test score, social class explained a much greater percentage of the variance. Among boys at the age of 7 years, social class explained 2.9% of the variance, and birth weight explained 0.8%. The corresponding percentages at age 11 were 9.9% and 1.4%, and the corresponding percentages at age 16 were 11.7% and 1.0%. Girls showed a similar pattern. Birth weight and social class had independent effects, but their trajectories appeared to diverge. The influence of birth weight remained constant over time, whereas social conditions played an increasingly important role with increasing age. The authors made an excellent attempt to control for confounding, but the results are still open to the possibility of residual confounding; for example, the relationship observed may have been due to an independent variable that affects both birth weight and cognition prenatally.

Newcastle Growth and Development Study and Performance Indicators in Primary Schools

The details regarding this unpublished study were provided by the authors in a manuscript that has been submitted for publication (Corbett, Durham, Wright, Tymms, & Drewett, 2004). In this study, data from two investigations were linked. The Newcastle Growth and Development Study identified all children born during a 1-year period (1987–1988) in Newcastle upon Tyne, England, and monitored their weight from birth through infancy. Gestational age and postcode (and therefore deprivation score, through the use of information from the 1991 census) were also recorded. The majority of this cohort of 3,655 participants also took part in the Performance Indicators in Primary Schools study, which involved biennial testing of educational attainment. At 10 years of age, participants completed a nonverbal test (the Problems of Position Test) and a verbal test (Picture Vocabulary Test); validation information on these tests was not included, although a reference was provided. A total of 2,294 (62.8%) of the Newcastle Growth and Development Study Cohort members were linked to Performance Indicators in Primary Schools results, and 2,030 (55.5% of the original cohort) had available birth weight information. Those who were not linked were similar to those who were in terms of birth variables, but they had lower deprivation scores.

Birth weights were provided in the form of age- and sex-standardized weighted standard deviation scores derived from the British Growth Standards. The lack of absolute values did not allow direct comparisons with other studies, but the overall raw correlation between birth weight and verbal ability test score was reported as .103 ($p < .01$). A figure was included showing that predicted mean scores for all ability tests increased with increasing birth weight to the 0–0.5 standard deviation category, with scores decreasing at the highest birth weights. Multiple regression results showed that contributors to Picture Vocabulary Test score included deprivation score ($R^2 = .16$, $p < .001$), birth weight ($R^2 = .009$, $p = .002$), and weight in late infancy ($R^2 = .004$, $p = .003$). Postnatal weight gain was the main focus of this study, and the authors concluded that the effect of early growth on cognitive outcomes in this population was largely attributable to prenatal growth. The study did not provide separate results for male and female children and did not include sex as a covariate. Also, no information was provided on birth order or parental characteristics. Gestational age was recorded in weeks or as term, whereas various other studies calculate gestational age in days. As mentioned, this study has not been published, and once it has undergone full peer review and been accepted for publication, the data presented may not include all of the details just described.

Summary of Studies Reviewed and Discussion

The six studies reviewed all showed a consistent relationship between birth weight and cognitive ability. We have described the strengths and weaknesses of each study to allow the reader to judge the confidence with which conclusions can be accepted. A statistical synthesis for such disparate studies would be inappropriate and misleading (Cochrane Non-Randomised Studies Methods Group, 2004), but the graphical display (see Figure 2) clearly shows that mental test score (not corrected for confounders) increases with increasing birth weight. The effect size difference between the lightest and heaviest groups is approximately 10 IQ points (Matte et al., 2001; Record et al., 1969). If this relationship is causal, an improvement in birth weight within this range could have an impact both at the individual level and, more significantly, in terms of populations. When confounders were corrected for in the analyses, most of the studies reviewed showed an attenuation of the relationship (e.g., Jefferis et al., 2002; Richards et al., 2002), but it remained statistically significant. Social class was the variable that explained the largest proportion of variance; however, when this variable was explicitly tested, it had an influence on cognition that was independent of birth weight (Shenkin et al., 2001).

All of the studies included births in the low birth weight range, and some of the results suggest that the association between birth weight and cognitive test score is mainly driven by those with the smallest birth weights (Record et al., 1969; Richards et al., 2002; Shenkin et al., 2001). However, a relationship was shown to persist even if those with birth weights below 2,500 g were excluded (Jefferis et al., 2002; Matte et al., 2001). Of interest, most of the data sets in which cognitive test scores were divided into categories showed a slight decrease in scores at the highest birth weights. This may have been due to these births occurring later in the birth order, and, in the study that corrected for birth order, there was no

longer a decrease in cognitive ability in birth weights above 5,000 g (Richards et al., 2002). However, this study was unable to correct for other factors related to increased birth weights such as gestational age or possible illnesses (e.g., diabetes). The most common cause of large (macrosomic) babies is maternal diabetes, and these babies are known to be at risk of perinatal complications; however, little information is available regarding their long-term outcomes, including cognitive abilities. This would be an interesting area for future study, and it has significant public health implications, particularly for the group of women now electing not to be routinely induced at 42 weeks of gestation. Also, mean birth weights are increasing.

As with all cohort studies, there was a potential for bias, and many of the studies considered used samples from selected hospitals or other groups, limiting their generalizability. The extent to which this situation was acknowledged varied among the studies. The ways in which the variables were measured was also a source of bias: We do not know the accuracy of birth weight measurements, and intelligence was assessed in a variety of ways, not all of which were validated adequately. Also, socioeconomic environment was assessed in a variety of ways, and the comparability of such measures between countries is difficult to assess. Assessment of children at different ages was a potential source of bias as well. In fact, looking at the variation among the studies, it is not surprising that there were some differences in the results; more remarkable is that there was some consistency. The reporting of consistent positive results may have been due to publication bias, but our extended searches did not identify any studies with nonsignificant results.

In view of the relationship between birth weight in the normal range and cognitive ability, ongoing study of underlying mechanisms is important. Both researchers and policymakers interested in maximizing the potential of children should consider influences acting early in a child's development and, indeed, factors affecting women of childbearing age. If the mechanisms underlying this association can be determined, they may be able to be targeted toward improving children's cognitive abilities.

Confounders and Confounding

Establishing whether or not a variable is part of a causal chain can be difficult, especially when the etiology is likely to be multifactorial, as in cognitive ability. Some of the variables identified in the studies discussed here as potential confounders may actually be part of the causal chain between birth weight and cognitive ability; for example, parental social class might affect fetal health through deprivation or tobacco use. This would mean that correcting for these so-called confounders would weaken or eliminate the association between birth weight and cognitive ability; however, rather than making the association irrelevant (which the term *confounder* can easily be taken to imply), it helps us to understand the mechanism of the association. In multivariate data sets in epidemiology, one variable tends to be selected as the dependent variable and one as the independent variable, and the rest are termed confounders, when in fact the interrelationships among these variables are likely to be more complex than this terminology implies. Statistical techniques more commonly observed in articles published in psychological than in medical journals, such as path analysis and structural equation modeling, can be useful in this situation. The Shenkin et al. (2001) study combined epidemiological and structural equation modeling analyses to examine possible confounding and mediation in the birth weight–IQ association.

Few of the reviewed studies included the data necessary to assess the relative contributions of confounders. The exceptions are as follows. According to Jefferis et al. (2002), the age 7 beta weight for birth weight (.17) was "little changed" (by less than .02) by the addition of gestational age, maternal age, social class, parity, breast feeding, or parental education. Birth weight R^2 values at the ages of 7, 11, and 16 years were .008, .014, and .010, respectively, for boys and .010, .015, and .011, respectively, for girls. The corresponding social class R^2 values were .029, .099, and .117 for boys and .027, .105, and .125 for girls. Shenkin et al. (2001) included social class ($\beta = -.26$, $R^2 = .066$), birth weight ($\beta = .20$, $R^2 = .038$), child's age ($\beta = .16$, $R^2 = .024$), parity ($\beta = -.15$, $R^2 = .020$), and illegitimacy ($\beta = .12$, $R^2 = .001$). Sex, birth length, maternal age, and gestational age were excluded from the model (*ns*). The overall R^2 value was .156. Corbett et al. (2004) included deprivation (R^2 change = .156), birth weight (R^2 change = .009), and weight in later infancy (R^2 change = .004). Gestation was not significant. The overall R^2 value was .16. These results suggest that socioeconomic environment has a relatively substantial association with childhood cognitive ability. Birth weight and other factors contribute smaller additional, independent variance. A large percentage (more than 80%) of the variance in childhood cognitive ability scores was not explained by these variables.

The Danish Metropolit 2000 study attempted to investigate the interrelationships among socioeconomic position, birth weight, and individual outcomes (Osler et al., 2003). The authors examined the relation between socioeconomic position in early life and mortality in young adulthood, taking birth weight and cognitive function into account. At the age of 12 years, 7,308 male singletons completed an IQ test (developed by Kell Härnquist and translated from Swedish). More boys in the lower birth weight categories fell in the lowest IQ test quartile (33.8% of those with birth weights below 2,500 g, 26.6% of those with birth weights between 2,500 and 3,499 g, and 28.9% of those with birth weights above 3,499 g). The birth weight categories were wide, and both birth weight and IQ were analyzed as covariates or mediators of the relationship between socioeconomic status and mortality. Low birth weight and low IQ were related to adverse socioeconomic position, and the relationship between socioeconomic position and mortality was attenuated when birth weight and IQ were included in the model. This suggested that birth weight and childhood IQ mediate some of the effect of socioeconomic position on mortality, therefore confirming our caution regarding use of the term *confounding* when dealing with birth weight and socioeconomic position.

Studies Not Included: Birth Weight and Adult Cognitive Ability

Three otherwise important studies were excluded because mental ability outcomes were assessed beyond participants' 17th birthday (Martyn, Gale, Sayer, & Fall, 1996; Seidman et al., 1992; Sorensen et al., 1997). These studies are mentioned here because

they add materially to our understanding of the possible reasons for the association between birth weight and intelligence. Also, as mentioned, one of the studies described earlier followed participants to the age of 43 years (Richards et al., 2002). Two studies tested cognitive ability at army conscription (Seidman et al., 1992; Sorensen et al., 1997). The results are described subsequently and illustrated in Tables 3 and 4 and Figure 4.

Jerusalem Perinatal Study

The first study (Seidman et al., 1992) followed 20,567 children who were born in a maternity ward in West Jerusalem, Israel, between 1964 and 1970 and who were drafted into the Israeli army at 17 years of age (exact ages were not reported). The analysis was restricted to male participants. Confounders examined were social class (municipal tax level and area of residence rather than paternal occupation), ethnic origin, maternal age, parental education, and birth order. Not included were, most important, gestational age and marital status, education, or any postnatal factors. There was no mention as to whether multiple births were excluded.

Results showed that mean IQ test scores increased with increasing birth weight (from 98.3, $SD = 14.9$, for those below 2,000 g to 103.0, $SD = 15.3$, for those between 3,500 and 4,000 g) but decreased beyond 4,000 g (to 100.8, $SD = 15.8$, for weights above 4,500 g; see Table 4 and Figure 4). When corrected for confounders, regression coefficients showed an increase in IQ with increasing birth weight, particularly in the lower birth weight categories (i.e., up to 3,000–3,500 g; −6.5 IQ points, $SE = 1.1$, for birth weights below 2,000 g and −3.6 IQ points, $SE = 0.6$, for birth weights between 2,000 and 2,499 g); the decrease at the higher values was no longer evident (see Figure 4). Multiple regression analyses showed that birth weight, ethnic origin, paternal education, maternal age, birth order, and social class together explained 22% of the variance in intelligence test scores. The authors acknowledged the risk of selection bias due to their lack of data on gestational age. The restriction of the sample to male participants limits the generalizability of the results. However, this study indicates that birth weight and social factors both have an influence on cognitive ability into adolescence.

Danish Conscripts Study

The second army recruitment study (Sorensen et al., 1997) was conducted in Denmark and involved boys born in 1973 and after and drafted at 18 years of age (again, exact ages were not reported). Of 5,183 men drafted, 4,661 underwent a medical examination (the others were excluded owing to illness), and 92.2% of these latter individuals ($n = 4,300$) were matched to their birth details. Whether this introduced any selection bias was not discussed, nor was whether multiple births were excluded. The test used, the Boerge Prien test, was reported to correlate highly with the Wechsler Adult Intelligence Scale. Mean scores (of a possible 78) on this test increased with increasing birth weight (from 39.9, $SD = 9.3$, among those with birth weights below 2,500 g to 44.6, $SD = 9.5$, among those with birth weights above 4,500 g; Table 4), flattening at the over 4,500 g birth weight category (see Figure 4).

When corrected for the confounders of gestational age, birth length, maternal age, parity, marital status, and employment status (employed, unemployed, or self-employed), mean scores increased with increasing birth weight from 1,900 to 4,200 g (data are not shown here but were illustrated graphically in the original article). There were some test score reductions at the highest weights, suggested as due to underlying disease or birth trauma. The social descriptors used were very crude, and there may have been important differences within employed groups that were not recognized. Other potential confounders that were not assessed included parental IQ and postnatal factors, and once again the results were restricted to male participants.

Preston and Sheffield Study

The smallest of these studies following participants into adulthood involved the longest follow-up (Martyn et al., 1996). Although it included both male and female singleton children, it involved a large potential for selection bias. Of those invited to take part in the study, 1,576 (47.5%) agreed, with very different uptake rates from different areas. Overall mean age was 60.9 years ($SD = 2.1$); in one area, however, the mean was 52.1 years ($SD = 0.6$), and in another it was 68.6 years ($SD = 1.4$). Participants completed Part 1 of the Alice Heim 4 test, estimating fluid intelligence, and the Mill Hill vocabulary test, estimating crystallized intelligence. Birth weight was reported in pounds (from less than 5.5 lb to more than 7.5 lb, equivalent to less than 2,500 g to more than 3,400 g); therefore, the range was restricted at the top end relative to most of the other studies discussed.

Results showed that mean Alice Heim Test (AH4) scores increased with increasing birth weight (from 20.8 among those below 2,500 g to 23.0 among those above 3,400 g [standard deviations were not reported]; see Table 4), but differences did not reach statistical significance. This association is not reported corrected for confounders, although the authors noted that similar results were achieved when excluding participants born before 38 weeks. An association was observed between biparietal diameter of the head at birth and AH4 score ($p = .008$) that persisted when corrected for age, social class, and individual data set (i.e., place of birth and current residence); scores increased by 3.7 points for each 2.5-cm increase in diameter. This may have been a Type I error, in light of the multiple correlations performed, but it raises the possibility of the use of other measurements at birth that may reflect insults to growth at different prenatal development stages.

In fact, a subsequent article (Gale, Walton, & Martyn, 2003) detailed the relationship between head size and cognitive function among 215 individuals born in Sheffield, England, between 1922 and 1930. This study also revealed no significant association between birth weight and AH4 score at a mean age of 69.8 years ($SD = 2.0$), as well as no association between head circumference (rather than biparietal diameter) at birth and score on AH4. It did, however, show an association between adult head size and test score, suggesting the importance of postnatal brain and head growth. Further studies are required to clarify the relative importance of birth weight and head/brain size at different stages of development.

British 1946 Birth Cohort

The 1946 birth cohort study (Richards et al., 2002) described earlier followed participants to the age of 43 years. Cognitive function increased with increasing birth weight up to the highest

birth weight category at the ages of 8 (various tests, as described earlier), 11 (verbal and nonverbal intelligence, arithmetic, word pronunciation, and vocabulary), 15 (AH4 test; $p < .001$), and 26 (reading comprehension $p = .001$) years. At age 26, the association was mainly attributable to those with birth weights below 2,500 g. Correction for confounders resulted in the association being more linear, and the effect persisted when analyses were restricted to those with birth weights above 2,500 g.

Conditional regression models showed that cognitive growth between the ages of 8 and 26 years was similar across all of the birth weight groups; thus, although the association persisted into adulthood, the effects of birth weight on test scores at ages 11, 15, and 26 were largely accounted for by its effect at age 8. At the age of 43 years, when up to 68% of those who had participated at 8 years of age were still involved, birth weight had no significant effect on test scores (i.e., verbal memory, search accuracy, and search speed). This finding may have been artifactual, resulting from the shift from psychometric tests of general ability to memory tests, or it could have been due to the increasing influence of adult environments or genetics.

Possible Causes: Lessons From Sibling and Twin Studies

Although all of the observational studies described here are in agreement that there is a small but statistically significant relationship between birth weight and intelligence, and this relationship persists after controlling for confounders, there is still a possibility that the relationship is due to residual confounding (i.e., confounders not measured or accounted for in the analyses). Sibling studies represent an attempt to control for the possible confounders present in observational studies. Such designs compare individuals with a shared family environment, although of course they will differ in their experiences outside the family.

Within the large cohort born between 1950 and 1954 in Birmingham, there were 5,042 sibling pairs (Record et al., 1969). There were restricted ranges of verbal reasoning score differences and birth weight differences within sibling pairs; the correlation between sibling verbal reasoning scores at age 11 was .55, and that between sibling weights was .50. It was necessary to standardize for sex (males are heavier but score less well) and birth order (later children tend to be heavier but score less well). A total of 2,049 pairs were removed from the analysis because their birth weights differed by less than 500 g, and the process of standardization removed a further 130 sibling pairs. Among the 2,312 pairs that differed in birth weight by 500 to 1,000 g, mean verbal reasoning scores differed by 0.3 points (heavier siblings scoring better); 518 pairs differed by 1,000 to 1,500 g, and the heavier siblings scored 0.4 points higher. In instances in which the difference was 1,500 g or more (33 pairs), the heavier siblings scored 1.5 points higher. Significance values and standard deviations were not presented; however, if a standard deviation of 15 is assumed and a t test is performed by hand, the differences in verbal reasoning scores between sibling pairs in each weight category are not statistically significant ($p > .10$). If only same-sex siblings with weight differences above 500 g are considered, mean differences in verbal reasoning scores between heavier and lighter siblings are 0.9 points for males and 0.7 points for females (again in a t test assuming a standard deviation of 15; $p > .10$). Record et al. (1969) concluded that "these data provide little evidence of variation in scores in relation to birth weight and duration of gestation within the same families. Hence the substantial variation [in the nonsibling group] is due to differences between rather than within families" (p. 79).

The National Collaborative Perinatal Project followed 59,000 pregnancies, and from this cohort Matte et al. (2001) analyzed data for 3,484 children from 1,683 families (1,567 families had two siblings, 114 had three siblings, and 2 had four siblings). This group was restricted to term births (37 weeks or more), to weights of 1,500–3,999 g, and to a birth order below five. The two-sibling sample included all sibling pairs along with a random pair from all families with more than two siblings. The WISC was used in measuring participants' cognitive ability at 7 years of age. Analyses, presented for only same-sex pairs, included birth weight differences of all magnitudes. Among boys, IQ differences were directly related to differences in birth weight. In a continuous linear regression analysis, boys showed an increase in IQ of 5.0 points (95% CI = 2.8, 7.1) for each 1,000-g increase in birth weight, whereas girls showed only a 1.0-point (95% CI = −0.9, 3.0) increase. An interaction model showed a significant interaction between sex and birth weight ($p = .008$). Categorical analyses confirmed these findings ($p < .001$ for boys and $p = .17$ for girls). Adjusting for birth order and maternal smoking did not affect the results. Adjusting for head circumference slightly reduced the effect of birth weight only. Limiting the analyses to those with birth weights above 2,500 g produced essentially identical results.

The fact that Matte et al. (2001) showed a statistically significant relationship between birth weight and IQ for male sibling pairs, whereas Record et al. (1969) found no significant difference, may be due to (a) the different inclusion criteria (Matte et al., 2001, excluded premature births and high birth orders), (b) the different test ages (7 years vs. 11 years), (c) the different tests used (the WISC, a validated IQ test battery, vs. a school verbal reasoning test), or (d) the different statistical methodologies. That the difference was significant only among boys may have been a Type I error, and this finding needs replication in other studies. It does, however, have some biological plausibility: Boys and girls exhibit different fetal growth rates and thus may respond differently to prenatal insults. This argument could be used to justify sex differences in either direction, and therefore future studies should specify whether sex differences are expected, and in which direction, before analyses are conducted.

The data from the sibling studies are inconsistent: The Record et al. (1969) study pointed toward the family/social environment explaining most of the relationship between birth weight and cognitive ability, but the Matte et al. (2001) study indicated that there is still some within-family association between birth weight and cognitive ability among boys. This could be a real effect of birth weight on intelligence, or it could still be due to confounding by nonshared within-family environments (e.g., individual intellectual stimulation or parent–infant relationships). Other within-family studies that may help to clarify this issue are twin studies.

Dizygotic twins essentially represent a special case of siblings: When reared together, they share the postnatal within-family environment, and there is no chance for the environment to change, as it could between siblings. The prenatal environment of twins must be highly correlated, and thus there is a very restricted range of between-twins variation in this environment. Any association observed between birth weight and cognitive ability in twins

would therefore be remarkable owing to the lack of power in these analyses and because the numbers involved are not large. A Dutch longitudinal study of 170 same-sex twin pairs (Boomsma, van Beijsterveldt, Rietveld, Bartels, & van Baal, 2001) showed associations between birth weight and IQ differences among dizygotic twin pairs (age 7: $r = .29$, $p = .01$; age 10: $r = .27$, $p = .02$). Also, when twins were ranked as heavier or lighter, there were statistically significant differences in IQ between dizygotic cotwins (approximately 2 to 4 IQ points) at 5, 7, and 10 years of age. These data are very persuasive that the relationship between birth weight and cognitive ability cannot be explained by within-family confounding variables.

One important potential explanation is mediation of the relationship by genetic factors. Dizygotic twins share 50% of their genes (as do siblings), whereas monozygotic twins have identical genetic material. Differences between monozygotic twins are therefore attributed to environmental rather than genetic influences. Among the monozygotic pairs in the Boomsma et al. (2001) study, there was no significant correlation between intrapair differences in IQ and birth weight at 7 and 10 years of age ($r = -.02$, $p = .88$, and $r = .01$, $p = .91$, respectively). This suggests that genetic factors mediate part of the association between birth weight and childhood IQ. However, at the age of 5 years, when twins were ranked as heavier or lighter, there was a statistically significant difference between monozygotic cotwins ($p = .01$). Differences were not statistically significant at other ages. Other researchers have reached conflicting conclusions. Scarr (1969) studied 25 monozygotic female twins between 6 and 10 years of age ($M = 7.9$ years) and did find a positive association between birth weight and IQ (as assessed by the Draw-a-Person Test). Differences in IQ varied from 5.4 points (when both twins were below 2,500 g) to 13.6 points (when one twin's birth weight was low). The mean difference in birth weight was 320 g. A similar pattern was seen in the Willerman and Churchill (1967) study but should also be viewed with caution owing to the small sample size. Owing to the lack of power inherent in these study designs resulting from the restricted variance, it is remarkable that these studies not only show a relationship but that it is consistent.

Overall, these studies suggest that the association between birth weight and cognitive function persists even when the family/social environment is held as constant as possible. The data are more persuasive for twin than sibling studies, with the caveat that the twin studies have involved small numbers. The fact that the association between birth weight and cognitive ability has been shown to be more pronounced for dizygotic than monozygotic twins suggests that genetic factors account for part of the association between birth weight and childhood ability. Genetic factors influence both intelligence (accounting for 40%–70% of the population variance; Deary, 2000) and birth weight, and thus they can be considered potential confounders in the relationship between birth weight and cognition. Further studies are required to confirm the relative roles of genetics and environment in the association between birth weight and intelligence. It is likely that this relationship will be complex, not just as a result of the polygenic nature of the inheritance of intelligence but also because the relative influences of genetics and environment will change throughout the life span. One caution from twin studies is that the intrauterine environment is so different for twins than singletons that conclusions from twin studies cannot be transferred to the general population (Morley, Dwyer, & Carlin, 2003).

Other Studies Not Included: Avenues for Future Research

The inclusion criteria used in this systematic review resulted in few studies being included in the full review. However, there are many large studies ongoing in which data have been collected on birth weight and childhood cognitive ability as well as various confounders. To be included in this review, studies had to be published or reported in the "gray" literature (e.g., technical or research reports, doctoral dissertations, discussion papers). Studies may not be published because (a) the relevant analyses have not been conducted, (b) the study design and analyses are not sufficient to pass peer review, or (c) the study is rejected on the basis of negative results. Because the design of observational studies is paramount in terms of minimizing bias, publication can be seen as a quality control mechanism designed to ensure that only the best studies are published. This is in contrast to randomized controlled trials in which all parameters other than the intervention of interest are controlled; if the results of all randomized controlled trials are summed, the true effect of the intervention can be calculated (Cochrane Non-Randomised Studies Methods Group, 2004).

There are many large cohorts available with the data necessary to investigate the birth weight–IQ association. Often, these data have been published as control data for a specific group being studied, but such control groups can be of interest in their own right (e.g., 1970 British birth cohort: small for gestational age $n = 1{,}064$, normal weight $n = 13{,}125$; Strauss, 2000; 1953 Stockholm cohort: low birth weight $n = 494$, normal weight $n = 12{,}079$; Lagerstrom, Bremme, Eneroth, & Magnusson, 1991; Swedish Birth Register, 1973–1978: low birth weight $n = 6{,}440$, normal weight $n = 233{,}531$, high weight $n = 6{,}785$; Lundgren, Cnattingius, Jonsson, & Tuvemo, 2001). These cohort studies could add to the body of evidence presented here and raise hypotheses to be tested in experimental designs. Some cohort studies have published results that take into account the relationship between birth weight and cognitive ability, but for methodological reasons, they were not included in this review. These studies are discussed in the following section.

The U.S. National Longitudinal Survey of Youth is a rich resource for many research questions. Three studies have used this survey to address issues relating to birth weight and cognitive ability. They were not eligible for the present systematic review because birth weight was assessed by means of mothers' recall, which has a large and unspecified potential for bias. However, because of the survey's large, nationally representative sample (with oversampling of African American children of highly educated parents), studies derived from it provide useful information. Two studies have used the National Longitudinal Study of Adolescent Health, a nationally representative survey of more than 90,000 adolescents 12–17 years of age in the school year 1994–1995. A subsample of these adolescents ($n = 20{,}745$) completed tests including the Picture Vocabulary Test (a verbal ability test), and of these participants 12,351 had mothers who recalled their birth weight. The first study (Rowe, 2002) investigated differences among verbal IQ, number of sexual partners, and birth weight in 14,702 adolescents with a mean age of 16 years (the standard deviation was not reported). Information on parental education, income, and racial group (both self-identified and categorized by the interviewer) was collected. IQ distributions for birth weight categories were not reported. Correlations between birth weight and IQ was reported as .06 ($p < .0001$) for White Americans and .04 ($p < .05$) for African Americans; however, there was no correction for confounders.

The second study (Gorman, 2002) involved a conscientious attempt to control for social influences. Only singleton births with full information were included, and this resulted in 9,994 participants, including 3,139 sibling pairs. There was an association between birth weight and Picture Vocabulary Test score (a 4.2-point difference between participants in the lowest and highest quintiles, or a regression coefficient of 1.10, $SE = .18$, in the ordinary least squares regression model, $R^2 = .01$, $p < .001$). When potential confounders (age, sex, duration of breast feeding, history of cigarette smoking, family structure, birth order, race, maternal age, parental education, and insurance coverage) were entered in the model, the association between birth weight and cognitive ability was attenuated (the mean regression coefficient was 0.54 [$SE = 0.13$], $p < .001$) but retained in the model ($R^2 = .26$). However, in analyses restricted to siblings (670 pairs), the regression coefficient was 1.01 ($SE = 0.36$, $p < .01$) when the analysis did not consider the relevance of the common sibling environment, falling to .18 ($SE = .34$, $p > .10$) when a fixed-effects model was used. This implies that in this group, as in the Record et al. (1969) study, there was no significant association between birth weight and cognitive ability when family characteristics were held constant. This study did not consider sex differences in the relationship (see Matte et al., 2001), and it was limited by the lack of gestational age data and the use of maternal recall of birth weights (and therefore the likelihood of recall bias). The differences in findings between these sibling studies and the twin studies require further investigation.

Another report from the National Longitudinal Survey of Youth was found in the extended searches. This PhD dissertation (Kiweon, 1992) was primarily concerned with the effect of poverty on children's academic performance, but it included birth weight as a covariate. The study used the merged child–mother data set, which includes 7,346 children born to mothers from the National Longitudinal Survey of Youth. Results of cognitive testing conducted in 1988 were reported. Age at testing (range = 5–18 years; $M = 8.3$, $SD = 2.4$, for Whites; $M = 8.7$, $SD = 2.6$, for Blacks). A total of 3,024 of the children completed the reading recognition section of the Peabody Individual Achievement Test. Reasons for the large loss to follow-up (up to 68.2%) were not discussed. Birth weight ranges and test results according to birth weight were not reported; however, mean birth weights were 3.33 kg ($SD = 0.57$) among Whites and 3.09 kg ($SD = 0.59$) among Blacks if the assumption is correct that the values reported are ounces. The important covariate of gestational age was not mentioned. The zero-order correlations between birth weight and reading recognition score were .095 for Whites and .088 for Blacks (similar results were obtained for reading comprehension and mathematics, all $ps < .001$).

Regression analyses are presented of multiple models testing the influence of various covariates. Similar patterns were found for all cognitive tests and among both races: There was a strong, direct (negative) relationship between poverty and test score, but this relationship was entirely accounted for by maternal cognitive ability, postnatal home environment, and birth weight. Child sex also contributed to the model (girls performed better). The final model explained less than 20% of the variance. Path analyses were performed to illustrate the significant effect of mother's cognitive ability both directly and indirectly, through birth weight and home environment. Birth weight and cognitive home environment both had a significant direct effect on performance; however, although poverty directly affected both of these variables, it did not have an additional direct effect on performance. Mother's cognitive ability also influenced time in poverty. This study is interesting in that it illustrates the importance of parental ability: Maternal ability was the variable exhibiting the strongest correlation (approximately .3) with children's performance. Therefore, socioeconomic class measures may exert their influence through parental ability and the creation of a nurturing postnatal environment, rather than poverty per se. The National Longitudinal Survey of Youth is a rich resource to investigate these questions further, particularly the importance of intergenerational influences. Future analyses should take into account the important confounders of gestational age and birth order and should consider losses to follow-up and validation of the data collected.

Matte et al. (2001) used data from the Collaborative Perinatal Study but included only a very small proportion of the births in their sibship sample. A report of the larger study (Hardy & Mellits, 1977) charted the distribution of IQ scores (as assessed by the WISC) at age 7 among 12,315 White and 13,352 Black children according to birth weight and gestational age. The graph included showed that IQ among term White children increased from about 93 for those with birth weights of 1,500 g or less to 103 for those with birth weights above 3,500 g. Among Black children, IQ scores increased from approximately 82 to 91 for the same birth weight categories. Although data on potential confounders were also presented graphically, this was not accounted for in the analyses. Again, this massive data set has great potential for further analyses.

The extended searches identified one small study published only in a PhD thesis (Allard, 1964). In this study, 526 children (261 female) from Guilford County, North Carolina, were selected from among 887 children taking part in the North Carolina Statewide Prekindergarten Program. Selection methods were not described. Children were tested at school at 9–12 years of age; they completed the Diagnostic Math Inventory and the Prescriptive Reading Inventory, and other educational outcomes, such as grade repetition, were recorded. Validation of these instruments was not described. There was a high risk of selection bias in this group, and gestational age was excluded from analyses because it was believed to be inaccurate. However, consistent with other studies, the birth weight correlation with math score was .14, and the correlation with reading score was .08. In multiple regression analyses, significant predictors of math scores were parental education, race, and birth weight, whereas for reading score only parental education, race, and sex were included in the model. This once again underlines the importance of considering intergenerational influences such as parental education on developing children.

Another study not included here was a review of the records of 2,383 infants born in Indianapolis in 1956, of whom 1,698 (71.3%) were traced and had data on physical and mental development questionnaires completed at the age of 9 years (Muller et al., 1971). The main focus of the study was the influence of perinatal

factors such as age of mother, presentation of baby, rupture of membranes, and achievement at school in terms of grades repeated and other developmental outcomes reported by parents, physicians, or school personnel. Children at one of the schools included (n = 537; 31.6% of those traced and 22.5% of the original cohort) completed the Lorge–Thorndike intelligence test. Validation of this test was not reported. In this selected population, test outcomes were crudely related to birth weight (weight < 2,500 g, n = 21, mean score = 15.43; 2,501–4,000 g, n = 456, mean score = 16.88; weight > 4,000 g, n = 60, mean score = 17.17), $F(2, 534) = 3.10$, $p < .05$. These data were not corrected for any confounders. There was no attempt to allow for the huge number of correlations performed; only those with significant results were reported. In view of these design and analysis limitations, this study can be seen as providing only weak support for a relationship between birth weight and intelligence.

A very important study that was not eligible for inclusion in the our review was the study of the outcomes of the Dutch Hunger Winter (Stein, Susser, Saenger, & Marolla, 1975). In this so-called natural experiment, children conceived and born in cities affected by a famine that took place during 1944 and 1945 were compared with those not exposed to the famine and with those conceived and born both before and after the famine. Ninety-six percent of male participants underwent cognitive testing (Raven's Progressive Matrices) at military induction when they were 18–19 years of age (n = 100,000+).

There were decreases in mean birth weight, but no differences in intelligence, between those exposed and not exposed to famine (the direct correlation between birth weight and cognitive test score was not reported). This gives no indication of an effect of prenatal famine exposure on mental performance. The authors considered possible mechanisms for this lack of association. First, babies who would have gone on to suffer mild mental impairment could have been at higher risk of mortality both during and shortly after the famine. Data from the study, however, were presented to refute this theory. Second, exposure to famine may have interacted with social environment to affect learning opportunities and thus performance. The authors reported that the data did not support such an interaction, although there was an association between social environment and mental performance. Importantly, fertility declined with the famine, particularly among members of lower social classes; this explained increases in overall test scores that were actually due to increases in the proportions of births in the higher social classes. The third explanation, believed by the authors to be most likely, was that there was sufficient brain reserve to protect functioning. Functional effects may ensue if the postnatal environment is suboptimal. The authors therefore suggested that postnatal influences have a more significant effect than prenatal conditions on mental abilities.

This study provides a strong argument that the association between birth weight and mental ability observed in other investigations was due to residual confounding as a result of social circumstances. However, because of the severity of deprivation in terms of macronutrients, micronutrients, and concomitant stress, mechanisms in the population exposed to famine may not be the same as those in other populations. This study underlines the fact that nonnutritional and postnatal influences should be considered in investigations of the association between birth weight and mental ability. Examples of nonnutritional influences are insulin-like growth factor (Berger, 2001) and stress hormones (Seckl, Cleasby, & Nyirenda, 2000), which have been implicated in both fetal growth and cerebral and synaptic development. We did not include any studies on the importance of the postnatal environment in this review, and of course socioeconomic and educational opportunities, along with nutrition and health, will affect infants' cognitive development (Kaplan et al., 2001).

Conclusion

The studies reviewed here do not definitively answer the question of whether birth weight within the normal range is related to childhood intelligence. They do all suggest a small, statistically significant relationship, but this may have been due to publication bias (i.e., studies producing nonsignificant results may not have been published or recorded in the gray literature), selection bias (people followed up in these studies may not be representative of the overall population), or residual confounding (the relationship may have been due to another variable not accounted for in the analyses, although, as discussed earlier, this may explain the mechanism rather than imply that it is irrelevant). Furthermore, there are suggestions that the relationship is not linear and that babies with very high birth weights may perform less well. Finally, there is some evidence that any such relationships may vary as children become older. Thus, several potential avenues remain for future study.

First, many large prospective studies with various primary aims have collected data on birth weight and childhood cognitive functioning, along with various confounders. These data should be analyzed and published, ideally in a form allowing comparison with existing studies, that is, including IQ scores for birth weight categories as well as correlation coefficients and multiple regressions, both uncorrected and corrected for confounders. Both birth weight and gestational age should be considered. In view of the differences between outcomes among boys and girls, it is important that studies either analyze the sexes separately or correct for sex. Also, researchers should make a point of examining the upper end of the birth weight distribution and its relationship with intelligence when corrected for birth order. It is important that data from babies born later than 1970 reach the literature, in that conclusions from the older studies reviewed here might or might not hold. Ideally, raw data should be combined in a national or international collaboration, but the investment of time and money required means that this is unlikely. Alternatively, or in addition, a national consensus is required in terms of follow-up study methodologies to allow comparisons between cohorts (Aylward, 2002b). This should be the case for normal or control groups as well as high-risk groups. It may be that more sensitive tests will reveal more subtle differences; for example, higher order verbal tests and more neuropsychologically oriented instruments have been suggested for studying high-risk births (Aylward, 2002a).

Other study designs will allow more rigorous tests of hypotheses generated from observational studies. Animal studies allow controlled manipulation of variables that may affect birth weight or cognition and may enable clinical research to focus on one area. Intervention trials such as randomized controlled trials conducted during pregnancy can test the effect of a specific intervention, but they rely on accurate identification of an appropriate intervention. Because birth weight may be merely a marker for underlying

etiological factors, randomized controlled trials involving many different nutritional and hormonal parameters may be relevant. Follow-up and pooling of completed and ongoing trials may provide information as to which interventions are (and are not) effective in influencing birth weight or cognition, or both (Ness, 2003). For example, intervention studies have shown that smoking cessation or nutritional supplements can improve birth weights by approximately 25 g but have raised concerns about the associated risks of cesarean delivery, maternal obesity, and a possible increase in cancer incidence among offspring (Joseph & Kramer, 2004). Because all interventions involve risk, there is insufficient evidence to make specific recommendations to pregnant women in terms of influencing the future of their unborn children (Gillman, 2002).

Second, it is clear that birth weight, even if it is confirmed to be a significant predictor of intelligence, will explain only a very small proportion of the variance, and therefore analyses should include estimates of the relative importance of all independent variables. To this end, methodologies familiar in psychology, but less so in medicine and epidemiology (e.g., path analysis/structural equation modeling), have great potential in this field. Such methodologies can also help to untangle potential confounders from mediators; most medical models treat all variables that may affect the independent and dependent variables as potential confounders, but if such variables are actually mediators, then a spurious correlation may be inferred (Aylward, 2002b). These methodologies can be useful as well in situations such as this, in which multicollinearity exists as a result of highly correlated predictor variables. Once the importance of the prenatal environment is established, further studies will need to assess the interactions of variables reflecting prenatal influences with early and late postnatal experiences. These interrelationships are likely to be complex, but only by perseverance and multidisciplinary collaboration can we hope to improve our understanding of early life influences on intelligence and thus help children achieve their potential.

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(Appendix follows)

Appendix

Search Strategies Used for Systematic Review

MEDLINE (1966–April 2003)

1. *birth weight/
2. birthweight.ti.
3. (birth adj5 weight).ti.
4. 1 or 2 or 3
5. cognition/
6. exp Mental Processes/
7. exp aptitude tests/ or exp neuropsychological tests/ or exp psychometrics/
8. Intelligence/
9. exp Educational Measurement/
10. Educational Status/
11. Child Development/
12. (cognit$ or education$ or intelligen$ or IQ).tw.
13. ((aptitude or neuropsychologic$) adj5 test$).tw.
14. or/5–13
15. 4 and 14
16. low.ti.
17. 15 not 16
18. 15 not 17
19. birth weight/or (birth adj5 weight).tw. or birthweight.tw.
20. *cognition/
21. exp *Mental Processes/
22. exp *aptitude tests/ or exp *neuropsychological tests/ or exp *psychometrics/ or *Intelligence/ or exp *Educational Measurement/ or *Educational Status/ or *Child Development/
23. or/20–22
24. 19 and 23
25. 24 not 15

EMBASE (1980–June 2003)

1. mental function/ or cognition/ or learning/ or aptitude/ or mental capacity/ or intelligence/ or intellect/ or intelligence quotient/ or mental development/ or cognitive development/ or mental performance/ or mental task/
2. aptitude test/ or intelligence test/ or mental test/ or neuropsychological test/
3. psychometry/
4. child development/
5. academic achievement/
6. (cognit$ or education$ or intell$ or IQ).tw.
7. ((aptitude or neuropsychologic$) adj5 test$).tw.
8. or/1–7
9. *birth weight/ or *fetus growth/
10. (birthweight or (birth adj5 weight)).ti.
11. 9 or 10
12. 8 and 11
13. 12 not low birth$.ti.
14. *mental function/ or *cognition/ or *learning/ or *aptitude/ or *mental capacity/ or *intelligence/ or *intellect/ or *intelligence quotient/ or *mental development/ or *cognitive development/ or *mental performance/ or *mental task/
15. *aptitude test/ or *intelligence test/ or *mental test/ or *neuropsychological test/
16. *psychometry/
17. *child development/
18. *academic achievement/
19. or/14–18
20. birth weight/ or fetus growth/
21. (birthweight or (birth adj5 weight)).tw.
22. 20 or 21
23. 19 and 22
24. 23 not 13
25. 24 not low birth$.ti.
26. 13 or 25

PsycINFO (1974–June 2003; Ovid)

1. birth weight/
2. (birthweight or (birth adj5 weight)).ti.
3. (low-birth$ or low birth).ti.

4. (1 or 2) not 3
5. (normal adj (birthweight or birth weight or weight at birth)).ti.
6. 4 or 5

ERIC (1965–April 2003; Ovid)

1. birth weight/
2. (birthweight or (birth adj5 weight)).ti.
3. (low-birth$ or low birth).ti.
4. (1 or 2) not 3
5. (normal adj (birthweight or birth weight or weight at birth)).ti.
6. 4 or 5

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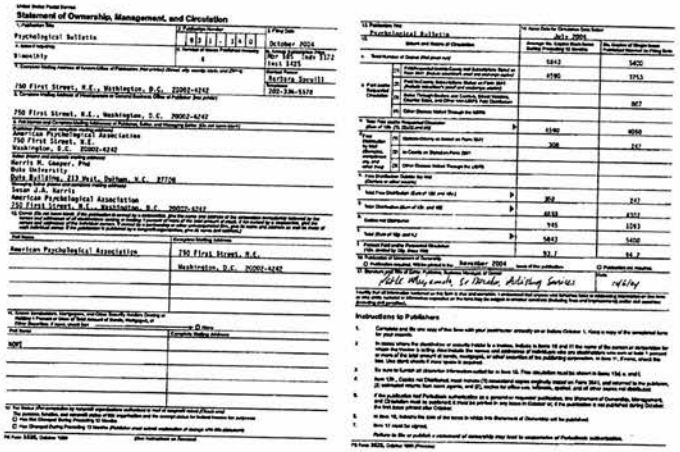

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Childhood and current cognitive function in healthy 80- year- olds: a DT-MRI study

Susan D. Shenkin,[1,2] Mark E. Bastin,[3,CA] Tom J. MacGillivray,[4] Ian J. Deary,[2] John M. Starr[1] and Joanna M. Wardlaw[5]

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Diffusion tensor (DT) MRI yields information on early pathological changes in white matter of the ageing brain which may correlate with cognitive function. However, because individuals vary in their cognitive ability, a measurement of prior cognition from youth is required to understand fully the significance of MR imaging changes associated with ageing. Here, diffusion tensor parameters and cognitive function were measured in a cohort of 30 older subjects whose cognitive ability was measured at age 11 and 80.

There was a significant correlation between diffusion anisotropy measured in the centrum semiovale at age 80 and mental ability determined at both age 11 and 80. These novel results suggest, that MR imaging studies of white matter structure and its relationship to mental ability in ageing should control for early life cognition. *NeuroReport* 14:000–000 © 2003 Lippincott Williams & Wilkins.

Key words: Ageing; Cognition; Diffusion; MRI; Tensor

INTRODUCTION

Cognitive decline is a widely recognized feature of normal ageing, but the underlying mechanisms which produce this progressive loss in cognitive function remain unclear. The concept of cortical 'disconnection', in which there is a disruption of white matter fibre tracks connecting cortical regions, has been proposed as a possible mechanism for this steady deterioration in cognitive ability [1,2]. Such a hypothesis finds support from post-mortem data which show that normal ageing is accompanied by the loss of small myelinated white matter fibres [3]. Unfortunately, the in vivo validation of this loss of brain structural integrity has, until recently, not been practical as conventional MRI is not sufficiently sensitive to detect subtle early pathology [4]. For example, white matter hyperintensities (WMH) visible on standard structural T_2-weighted MR imaging have been found to correlate inconsistently with cognition and ageing [5].

With the introduction of diffusion tensor (DT) MRI, however, it is now possible to map white matter fibre tracks non-invasively and determine how brain connectivity is altered in ageing and disease. In this technique, the apparent diffusion tensor of water (**D**) is calculated for each voxel in an image from sets of diffusion-weighted MR images [6]. Diagonalizing **D** produces eigenvalues and eigenvectors, the effective principal diffusivities along the orthotropic axes of the tissue, which can be used to measure the mean diffusivity ($\langle D \rangle$) and diffusion anisotropy indices, such as the fractional anisotropy (FA) [7]. Values of $\langle D \rangle$ indicate the magnitude of water molecule diffusion, while FA provides a scalar measure of the deviation from pure isotropic diffusion of water mobility in vivo. Due to the presence of axonal membranes and myelin. water molecules diffuse preferentially along axons rather than across them [8]. These diffusion tensor parameters are therefore thought to provide useful markers of white matter fibre tract integrity, with low values of $\langle D \rangle$ and high values of FA indicating intact healthy neurons [2]. This simple, argument in conjunction with the cortical disconnection theory then implies that $\langle D \rangle$ should have a negative correlation and FA a positive correlation with cognitive ability.

Several recent DT-MRI studies have found some evidence for white matter track disruption in normal ageing. For example, Nusbaum *et al.* [9] measured a statistically significant decrease in diffusion anisotropy of periventricular white matter, frontal white matter and the corpus callosum with increasing age in a group of 20 healthy volunteers aged between 20 and 91. O'Sullivan *et al.* [2] also found that diffusion anisotropy was reduced and fell linearly with age in the white matter of 20 volunteers aged 56–85 compared with 10 younger controls. These differences were maximal in frontal regions. Furthermore, in the older subjects they found that anterior $\langle D \rangle$ and parietal FA correlated with executive function as determined by the Trail Making and Verbal Fluency tests. Thus, the O'Sullivan study suggests the possibility that white matter structural changes occurring during the normal ageing process may affect cognitive ability.

Such cross-sectional studies reporting correlations between cognition and MR imaging parameters in older subjects must, however, take account of the stability of cognitive differences [10]. Specifically, individuals vary in their cognitive ability, so validating the relationship between diffusion tensor parameters and age-related cognitive change requires additional information about previous mental performance. Ideally, such cognitive data would include information on childhood mental ability, since brain development may be a key process in determining cognitive ageing. For example, low childhood IQ has been shown to be a risk factor for late-onset dementia [11]. Although childhood cognitive ability can be estimated using the National Adult Reading Test (NART) [12], an actual record of previous performance would be far better. In this paper we report results from a DT-MRI study of a unique cohort of older subjects whose cognitive ability was measured at age 11 and 80. Statistical analyses were performed to investigate whether diffusion tensor parameters correlate with cognitive performance only in old age, or with performance on the same test taken in both early and later life. If childhood cognitive ability is found to be important then it would have significant implications for future imaging studies of age-related cognitive decline.

MATERIALS AND METHODS

Thirty subjects (15 male, 15 female) who were living independently and had previously taken part in the Scottish Mental Survey of 1932 at age 11 were recruited at age 80 (mean (±s.a.) 79.8±0.4 years) into this study. This cohort then underwent neurological and cognitive testing, and brain MR imaging. The study was approved by the local ethics committee and in all cases informed consent was obtained.

Cognitive tests: Early life cognitive ability was assessed in these 80-year-old subjects by the Scottish Mental Survey of 1932 (SMS 1932). The SMS 1932 tested almost all Scottish 1921-born schoolchildren on 1st June 1932 (population 87 498). The mental test was a version of the Moray House Test (Number 12) used for school selection at age 11, and is referred to as MHT 1932. It has previously been shown to correlate at a level of about 0.8 with the Stanford-Binet test in 1000 pupils tested in 1932 [10]. Early life ability was also estimated using the NART, which involved reading 50 irregularly-pronounced words [12]. To assess later life cognitive ability, subjects retook the MHT in 2001 (MHT 2001) and were further examined to provide measures of global cognitive function (mini mental state examination. MMSE) and executive function (verbal fluency estimated using the Controlled Word Association test [13]).

MRI: All MRI data were obtained using a GE Signa LX 1.5 T. (General Electric, Milwaukee, WI, USA) clinical scanner, equipped with a self-shielding gradient set (22 mT/m maximum gradient strength and 120 T/m/s slew rate) and manufacturer-supplied birdcage quadrature head coil. To identify silent brain pathology each patient underwent standard structural MR imaging, namely axial T_1-weighted spin-echo, T_2-weighted last spin-echo (FSE) and FLAIR FSE. This was followed by a DT-MRI protocol that has been described previously [14]. The duration of the examination was 40 min.

In the DT-MRI experiment diffusion-weighted (DW) images were acquired using a single-shot spin-echo echo-planar (EP) imaging sequence in which two symmetric trapezoidal gradient pulses of duration δ=32.2 ms, separation Δ=39.1 ms and rise time η=1.2 ms were inserted around the 180° refocusing pulse in the required gradient channel. Sets of axial DW-EP images (b=0 and 1000 s/mm^2) were collected with diffusion gradients applied sequentially along six non-collinear directions [15]. Five acquisitions consisting of a baseline T_2-weighted EP image and six DW-EP images, a total of 35 images, were collected per slice position. The acquisition parameters for the DW-EP imaging sequence were 21 axial slices of 5 mm thickness and 1.0 mm slice gap, a field-of-view of 240 × 240 mm, an acquisition matrix of 128 × 128 (zero filled to 256 × 256), a TR of 10 s and a TE of 98.8 ms.

Image analysis: All the DICOM format magnitude images collected in each examination were transferred from the scanner to a Sun Ultra Spare Station 10 (Sun Microsystems, Mountain View, CA, USA) and converted into Analyze (Mayo Foundation, Rochester, MN, USA) format using in house software written in C. The following computations were then performed using the Matlab programming environment (The Mathworks, Natick, MA, USA).

In the DT-MRI experiment the set of five component DW-EP images for each gradient direction was averaged to give seven high signal-to-noise ratio images for each slice. Geometric image distortions arising from the strong eddy currents created by the diffusion gradients were then corrected in the six averaged DW-EP images using a modified version of the iterative cross-correlation algorithm [16]. Within each voxel the six elements of **D** and the T_2-weighted signal intensity were estimated by multivariate linear regression from the signal intensities measured in the DW-EP images [6]. After diagonalization of **D** to yield the magnitude sorted eigenvalues (λ_i), maps of the T_2-weighted signal intensity, the mean diffusivity

$$\langle D \rangle = \mathrm{Trace}(\mathbf{D}/3) \frac{\lambda_1 + \lambda_2 + \lambda_3}{3} \quad (1)$$

and the fractional anisotropy [7]

$$FA = \sqrt{\frac{3}{2}} \sqrt{\left[\frac{(\lambda_1 - \langle D \rangle)^2 + (\lambda_2 - \langle D \rangle)^2 + (\lambda_3 - \langle D \rangle)^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2} \right]}. \quad (2)$$

were generated on a voxel-by-voxel basis and converted into Analyze format. The FA measures (he fraction of the total 'magnitude' of **D** that is anisotropic, and takes a value of 0 for isotropic diffusion (λ_1=λ_2=λ_3) and 1 for completely anisotropic diffusion ($\lambda_1 > 0$; λ_2=λ_3=0).

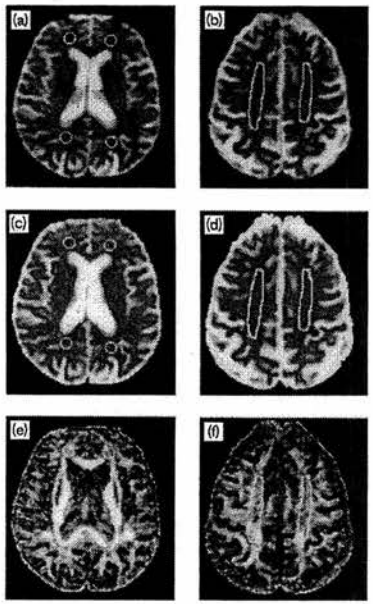

Fig. 1. Maps of T_2-weighted signal intensity (**a**, **b**), ⟨D⟩ (**c**, **d**) and FA (**e**, **f**) obtained at the level of the body of the lateral ventricles and centrum semiovale in an 80-year-old female subject. These images show the typical location of ROI defined on the T_2-weighted EP images, and used to measure ⟨D⟩ and FA in normal-appearing frontal and occipital periventricular white matter and centrum semiovale.

A region-of-interest (ROI) analysis was then performed for normal-appearing white matter following the approach described by O'Sullivan *et al.* [17]. So that the observer was not influenced by values of ⟨D⟩ and FA, all ROI were defined on the T_2-weighted EP images. Values of ⟨D⟩ and FA for normal-appearing frontal and occipital periventricular white matter were obtained from multiple small circular (69 voxels, volume 303 mm^3) ROI placed near the anterior and anterior and posterior horns of the lateral ventricles (Fig. 1a). Several larger, oval ROI (typically 500 voxels, volume 2197 mm^3) were also placed in normal-appearing centrum semiovale (Fig. 1b). Partial volume effects were minimised by siting the ROI at least 3 voxels from both the edge of the ventricles and abnormally appearing white matter. Since the T_2-weighted EP images and the DT-MRI parametric maps were by definition co-registered, this allowed ⟨D⟩ and FA values to be measured simultaneously in each ROI. The observer (TJM) was blind to the clinical status and cognitive function of participants, and purpose of the study. In addition, white matter lesion load was quantified independently using a recognised scale by a radiologist (JMW) blinded to cognitive and DT-MRI results [18].

RESULTS

Of the 30 subjects enrolled in this study, DT-MRI data were obtained from 28 subjects (13 male, 15 female), with one imaging examination excluded due to technical problems and another due to silent pathology (an incidental meningioma). Cognitive data were obtained from 27 subjects, with one blind woman being excluded. Due to the age of this population, a number of subjects displayed regions of diffuse WMH on T_2-weighted MR imaging. On the Fazekas scale [18], periventricular WMH ranged from 1 to 3 (median 2, inter-quartile range 1–2), while deep WMH ranged from 0 to 3 (median 1, inter-quartile range 1–1) indicating mostly mild white matter changes.

Table 1 shows that the values for male ⟨D⟩ are slightly higher, and FA lower, than females in almost all regions measured. This difference is not, however, statistically significant ($p > 0.05$) as determined by an independent samples *t*-test (equal variance not assumed).

Descriptive statistics for the cognitive test results in this population are presented in Table 2. Table 2 also shows that the correlations between diffusion tensor parameters and the cognitive rests are mostly in the direction of better performance associated with lower ⟨D⟩ (negative correlation) and higher FA (positive correlation). There is a significant association between centrum semiovale FA and actual childhood ability determined from the MHT 1932 (ρ=0.42, p=0.03) and estimated childhood ability determined from the NART (ρ=0.46, p=0.01). This association is similar for MHT 2001 (ρ=0.41, p=0.03). However, it is less strong and non-significant for ability assessed using the MMSE and verbal fluency tests. A strong negative correlation is also observed between centrum semiovale ⟨D⟩ and MMSE (ρ=−0.41, p=0.03). There is only one statistically significant association for frontal white matter, namely between FA and MHT2001 (ρ=0.51, p=0.01), and none for the occipital regions.

DISCUSSION

If one accepts the principle of parallel distributed cortical processing networks as a basis for cognition [20], then the hypothesis that diffusion tensor parameters have a relationship to cognitive function rests on the assumption that ⟨D⟩ and especially FA provide markers of white matter fibre tract integrity. Results from tortuosity models of water diffusion in the extracellular space and measurements of tetramethylammonium ion diffusion in rat brain suggest that values of ⟨D⟩ observed at typical levels of diffusion-weighting ($b < 1500$ s/mm^2) probably reflect the mobility of the extracellular water component [8,21,22]. Furthermore, extensive in vivo and in vitro experiments on various non-myelinated neuronal fibres [23,24], axons with large axoplasmic spaces [25] and neurons in which fast axonal transport has been inhibited [23], indicate that the primary determinant, of white matter anisotropic diffusion is the dense packing of axonal membranes with myelin playing a secondary role. Thus, the values of ⟨D⟩ and FA reported in most current DT-MRI studies probably principally reflect the hindering water mobility and anisotropic tortuosity of the interstitial space. Early age-related pathological changes, such as the loss of small myelinated white matter fibres [3], might be expected to alter the structural organisation and/

Table 1. Mean ± s.d. values of diffusion tensor parameters in normal-appearing white matter in 13 male and 15 female volunteers aged 80.

	⟨D⟩ ($\times 10^{-3}$) mm^2/s)			Fractional Anisotropy, FA		
	Male	Female	Total (n=28)	Male	Female	Total (n=28)
Frontal white matter	0.868 ± 0.063	0.835 ± 0.035	0.850 ± 0.052	0.31 ± 0.02	0.32 ± 0.02	0.32 ± 0.02
Occipital white matter	0.798 ± 0.042	0.763 ± 0.025	0.799 ± 0.038	0.39 ± 0.04	0.41 ± 0.04	0.40 ± 0.04
Centrum semiovale	0.796 ± 0.070	0.767 ± 0.030	0.781 ± 0.053	0.40 ± 0.06	0.40 ± 0.04	0.40 ± 0.05

Table 2. Descriptive statistics for the cognitive test results and correlations between diffusion tensor parameters of normal-appearing white matter and cognitive ability (Spearman's ρ). Bold type denotes $p < 0.05$.

Cognitive ability	Descriptive statistics			Frontal white matter				Occipital white matter				Centrum semiovale			
				⟨D⟩		FA		⟨D⟩		FA		⟨D⟩		FA	
	Man ± s.d.)	Min	Max	ρ	p	ρ	p	ρ	p	ρ	p	ρ	p	ρ	p
Childhood															
MHT 1932	43.74 (± 13.99)	16	67	0.00	0.99	0.34	0.08	−0.12	0.55	0.10	0.61	−0.07	0.71	**0.42**	**0.03**
Estimated prior NART*	29.36 (± 9.50)	12	44	−0.06	0.77	0.15	0.44	−0.09	0.63	−0.08	0.67	−0.17	0.38	**0.46**	**0.01**
Age 80															
MHT 2001	55.04 (± 8.04)	42	71	0.06	0.78	**0.51**	**0.01**	−0.18	0.35	0.07	0.71	−0.06	0.76	**0.41**	**0.03**
MMSE	27.96 (± 1.43)	25	30	−0.13	0.52	0.17	0.39	−0.18	0.38	0.14	0.47	**−0.41**	**0.03**	0.28	0.15
Verbal fluency	35.18 (± 11.01)	18	59	−0.02	0.93	−0.31	0.11	−0.12	0.56	0.19	0.33	−0.11	0.58	0.20	0.30

*The NART is coded by subtracting the error score from 50. The score indicates a mean IQ of ~110. The minimum of 12 is equivalent to an IQ of 96, and maximum of 44 equivalent to an IQ of 123 [12]. This sample has a higher mean IQ (approximately 9 points) but similar SD to the population of 87,498 children who took the MHT in 1932 (34.46 (15.5)) [19].

or reduce the density of axonal membranes. Such 'ultrastructural' changes would result in an increase in ⟨D⟩ and reduction in FA compared with values measured in normal young brain, exactly as reported by Nusbaum [9] and O'Sullivan [2]. However, as discussed by O'Sullivan *et al.*, the weak point of current DT-MRI methodology lies not in the validity of using FA as a marker for white matter tract integrity, but rather in the way such parameters are actually measured. Specifically, while an ROI based analysis is a convenient way of measuring ⟨D⟩ and FA, it provides only a crude estimate of true white matter connectivity. This is because functionally important fibre tracks may occupy only a small sub-region of the chosen ROI. Alternatively, it could be argued that the larger the ROI the more chance there is of including data from such functionally important fibres. This may be why an association between FA and cognitive ability was principally found in centrum semiovale in the current study. This structure is larger and therefore more likely to contain a greater number of functionally important fibre tracts than smaller frontal and occipital white matter regions. In future it may be possible to address such problems directly by tracking the relevant fibre projections from the diffusion tensor data [26].

O'Sullivan *et al.* [2] used the NART to estimate early life cognitive ability. The current study is unique in that, an *actual* measure of premorbid intelligence has been used. The similarity in the correlations observed between centrum semiovale FA measured at age 80 and actual childhood and estimated prior cognitive ability suggest that the NART may be a valid indicator of premorbid intelligence with respect to diffusion anisotropy indices. This is an important point as most researchers will not have access to a measure of actual childhood mental ability.

A particular strength of the current study is that data has been collected from older people within a very narrow age range, and longitudinally across a very long time period. The association between diffusion tensor parameters and cognitive function measured in a group of subjects all aged 80 indicates that there is variability among older individuals that does not merely reflect chronological age. Furthermore, the fact that diffusion tensor parameters correlate with cognitive function assessed at both age 11 and 80 implies that values of ⟨D⟩ and FA measured in later life probably predominantly reflect developmental differences in white matter established at an early age rather than current pathology.

This study was exploratory and by investigating several correlations in a relatively small population could be prone to type I errors. Bonferroni correction can be used to minimise type I errors, and after such correction the correlations indicated in Table 2 no longer reach conventional statistical significance. However, the appropriateness of this method, especially when the variables are not truly independent, is debatable [27]. Furthermore, the consistency of the results showing an association between centrum semiovale FA and cognitive ability in childhood (measured and estimated) and in old age suggests that these findings may not be due to just chance and require further investigation in larger populations.

Finally, it should be noted that many of the subjects had evidence of diffuse areas of WMH on T_2-weighted MR imaging. Although care was taken to avoid these regions, it is not possible to exclude the possibility that small abnormal regions were included in the chosen ROI, especially in cent rum semiovale. This is problematic given that the relationship between the presence of WMH and cognitive function

is yet to be fully elucidated. For example, while O'Sullivan *et al.* [17] found that increased ⟨D⟩ and decreased FA in white matter correlated with executive function in people with clinical lacunar events, in another group of 80 year olds WMH was found to be related to old-age but not childhood cognitive function [28]. Clearly more work is required to investigate how MR imaging parameters, both quantitative (*e.g.* ⟨D⟩ and FA) and qualitative (e.g. T_2-weighted signal intensity), relate to cognitive ability in all age groups.

CONCLUSION

In this study evidence has been found for a relationship between diffusion tensor parameters measured in centrum semiovale and performance on the same cognitive test undertaken in both early life and old age. The significant correlation between white matter diffusion anisotropy measured at age 80 and cognitive function assessed at age 11 is novel, and was confirmed by estimation of earlier ability using the NART. These results imply that considering adult cognitive ability without knowing childhood cognition may obscure the aetiology of MR imaging changes associated with ageing. Larger studies are now needed to replicate these findings, and to investigate further the relationship between diffusion tensor parameters and cognitive function from childhood to old age.

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Birth weight and cognitive function at age 11 years: the Scottish Mental Survey 1932

S D Shenkin, J M Starr, A Pattie, M A Rush, L J Whalley, I J Deary

Abstract

***Aims*—To examine the relation between birth weight and cognitive function at age 11 years, and to examine whether this relation is independent of social class.**

***Methods*—Retrospective cohort study based on birth records from 1921 and cognitive function measured while at school at age 11 in 1932. Subjects were 985 live singletons born in the Edinburgh Royal Maternity and Simpson Memorial Hospital in 1921. Moray House Test scores from the Scottish Mental Survey 1932 were traced on 449 of these children.**

***Results*—Mean score on Moray House Test increased from 30.6 at a birth weight of <2500 g to 44.7 at 4001–4500 g, after correcting for gestational age, maternal age, parity, social class, and legitimacy of birth. Multiple regression showed that 15.6% of the variance in Moray House Test score is contributed by a combination of social class (6.6%), birth weight (3.8%), child's exact age (2.4%), maternal parity (2.0%), and illegitimacy (1.5%). Structural equation modelling confirmed the independent contribution from each of these variables in predicting cognitive ability. A model in which birth weight acted as a mediator of social class had poor fit statistics.**

***Conclusion*—In this 1921 birth cohort, social class and birth weight have independent effects on cognitive function at age 11. Future research will relate these childhood data to health and cognition in old age.**

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Keywords: birth weight; Barker hypothesis; social class; intelligence

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Intelligence is determined by a combination of genetic and environmental influences, the relative contributions of which are not yet established, and may vary over the lifespan.[1] Environmental influences originate while the fetus is developing in utero. The "fetal origins" or "programming" hypothesis[2] proposes that these influences cause permanent changes in the developing child, resulting in low birth weight, and a predisposition to chronic disease in adult life. The mechanism of this relation is suggested to be fetal undernutrition, with even brief periods of undernutrition during critical periods of rapid cell division causing permanent changes in various organs.[2] Malnutrition in utero affects brain development,[4] and the relation between birth weight and cognitive function has therefore been studied.

It has been known for many years that "low birth weight" or intrauterine growth restricted babies fare less well on various measures of mental development in later life.[5] Many studies have compared low birth weight babies (<2500 g) with controls, showing impairment in various neurodevelopmental tests up to age 11.[5–7] Recent large longitudinal cohorts have allowed assessment of the relation between birth weight differences within the normal range and later differences in cognitive function.[8–11] These show that lower birth weight is associated with lower scores on tests of cognitive function at age 8 in the general population,[8] and at age 17–18 in army recruits.[9 10] A relation between birth weight and cognitive function was also seen through childhood to middle life,[8] but was largely explained by the influence of birth weight on cognition at 8 years. A study of older adults (mean age 60.9), which estimated early life mental ability, found the association between birth weight and cognitive function to be not significant[11] (corrected for age and social class). Martyn *et al* therefore suggest that fetal growth is less important than genetic factors and postnatal environmental influences in determining adult cognitive performance.[11]

A recent review concluded that intrauterine growth restriction had little clinically significant effect on mental performance in childhood or adolescence, but was a useful surrogate for social deprivation.[12]

Much of the criticism surrounding the programming hypothesis concerns the confounding influence of factors other than fetal undernutrition operating perinatally and throughout life.[13] In particular, the socioeconomic environment in which a child is conceived and develops will have an effect on both their physical[14] and mental[13] development. Another important potential confounding factor between birth weight and mental ability is gestational age: without this information, many studies have been unable to distinguish low birth weight caused by prematurity from "small for gestational age" or "intrauterine growth restriction".[7 15] When investigating early life influences on cognitive development, it is therefore important to consider the combination of birth weight and gestational age.[16] The relation between birth weight and placental weight[17] might also be relevant. There is also a suggestion of a non-linear relation between birth weight and intelligence, with relatively low cognitive performance at the highest birth weights.[9 10]

There is therefore a need for further studies of birth weight and childhood intelligence to address these issues. Furthermore, if studies from different historical time periods find a consistent relation, this will increase the generalisability of their conclusions. Here we report on a well characterised sample from a distinct historical period. The sample's cognitive function at age 11 may be compared with that of all 11 year old children in Scotland as a result of the Scottish Mental Survey 1932; gestational age can be calculated; and there is information on socioeconomic status. We tested the competing hypotheses that birth weight: (1) is related to cognitive function at age 11 independent of socioeconomic status; and (2) acts as a mediator of the effect of socioeconomic status on cognitive function at age 11. We also assessed the contribution of other features of the child (for example, gestational age, placental weight, age at cognitive test) and mother (age, parity) to later cognitive function.

Subjects and methods

BIRTH DATA

Detailed records of all admissions to the Edinburgh Royal Maternity and Simpson Memorial Hospital in Scotland have been retained in the Lothian Health Services Archive at the University of Edinburgh. The records for 1921 include date of birth, last menstrual period (from which gestational age can be calculated), previous pregnancies, maternal age and address, paternal occupation (if father known), birth weight and length, and placental weight. The records for admissions not relating to a live delivery were excluded, as were records for twins. This left 985 live singleton births.

MENTAL ABILITY DATA AGE 11

The Scottish Mental Survey was administered under the auspices of the Scottish Council for Research in Education (SCRE) to all children in Scotland at school on 1 June 1932, and born in 1921 (n = 87 498; 44 210 boys, 43 288 girls).[18] This test was closely related to the Moray House Test Number 12 used in the "11-plus" in England, and will be referred to hereafter as the Moray House Test (MHT). Only a small number of children at private schools, or those absent because of sickness, were not tested. The maximum possible Moray House Test score was 76, from 71 items. The scores were concurrently validated by individually retesting a representative sample of 1000 children on the Stanford Revision of the Binet–Simon Scale ($r = 0.8$).[19] SCRE made the complete set of 1932 data available for these analyses.

Hospital birth records from 1921 were matched with subjects' records from the Scottish Mental Survey 1932. The subject's full name was identified by tracing the original birth certificate, and a match was confirmed when full name and date of birth were identical. A match was obtained in 449 cases (45.6%).

STATISTICAL ANALYSES

Birth weight and other variables, even when they were distributed along continua, were divided into categories in some analyses for the purposes of description and comparison with previous studies.[9–11] Models of association were tested initially by partial correlation, with birth measurements used as continuous, not categorical variables. These are reported initially unadjusted, and then adjusted for gestational age, maternal age, parity (total number of previous pregnancies), legitimacy of birth, exact age (in days), and social class. Social class was assigned from the husband's stated occupation (if available) according to the standard occupational classification for the Office of Population Censuses and Surveys (OPCS 1990) and by the General Register Office Classification of Occupations. Analysis by both methods gave similar results (available from the authors) and the General Register Office Classification is reported here. Legitimacy of birth was included as a surrogate social class variable, as no social class could be allocated where the father was not known. It is likely that an unmarried woman with a child in the 1920s would suffer greater social disadvantage than she would today. Stepwise multiple linear regression analysis was performed, with Moray House Test score as the dependent variable. All independent variables significant at the 0.05 level were added to the models. Results for male and female children were calculated separately and in combination. In view of previous reports of a decline in mental ability in those with highest birth weights,[9] the data were re-examined, setting a birth weight limit of 4200 g (the point after which intelligence score was not related to birth weight in Sorensen *et al*).[9] Data were analysed using the SPSS statistical software package (SPSS version 10.0; SPSS Inc., Chicago, Illinois, USA, 1999). Structural equation modelling was performed using the EQS programme[20] to test competing hypotheses concerning the effects of birth weight and socioeconomic status on mental ability at age 11.

Results

DESCRIPTIVE STATISTICS

The performance of the sample on the MHT (n = 449: 246 boys, 203 girls; mean MHT score 36.9, SD 14.9) was significantly better than the general Scottish population (mean MHT score 34.5, SD 15.5; $p < 0.001$), although the effect size of the difference was small (table 1). Therefore, the present sample is not unusual with respect to the population's mean and spread of mental ability test scores at age 11 years. Table 2 divides the hospital births into those whose scores were traced, and those whose scores were not. Of the children whose scores were traced, 54.8% were male, compared with 47.6% of the total

Table 1 Comparison of Moray House Test scores: sample born in Royal Maternity and Simpson's Memorial Hospital, and Scotland

	Male		Female		Total	
	Sample	Scotland	Sample	Scotland	Sample	Scotland
Number (%)	246 (54.8)	44 210 (50.5)	203 (45.2)	43 288 (49.5)	449	87 498
Mean (95% CI)	36.8 (35.0 to 38.6)	34.5 (34.3 to 34.7)	37 (34.9 to 39.1)	34.4 (34.3 to 34.5)	36.9 (35.5 to 38.3)	34.5 (34.3 to 34.6)
p value	<0.02		<0.002		<0.001	

($p < 0.05$). Of these children 84.2% were legitimate, compared with 61.8% of the total ($p < 0.001$). They were more likely to have an older mother ($p = 0.001$), be later in the birth order ($p = 0.009$), and longer ($p = 0.007$). There was no difference in social class distribution between the two groups.

BIRTH CHARACTERISTICS AND MENTAL ABILITY

Mean (SD) scores on MHT test for each category of birth measurements are reported (table 3), both uncorrected, and then corrected for gestational age, maternal age, parity, social class, and legitimacy. Here we also report the correlation corrected only for social class. Birth weight was significantly related to the Moray House Test score (uncorrected: male $r = 0.15$, $p = 0.02$; female $r = 0.21$, $p = 0.03$; total $r = 0.17$, $p < 0.001$; corrected for social class ($n = 395$): male partial $r = 0.21$, $p = 0.02$; female partial $r = 0.22$, $p = 0.02$; total partial $r = 0.22$, $p < 0.001$; corrected as above ($n = 295$): male partial $r = 0.23$, $p = 0.003$; female partial $r = 0.27$, $p = 0.002$; total partial $r = 0.25$, $p < 0.001$), as was birth length (corrected as above: male partial $r = 0.11$, $p = 0.14$; female partial $r = 0.17$, $p = 0.05$; total partial $r = 0.14$, $p = 0.01$). Birth length was no longer significant when controlled for birth weight (birth weight and length were significantly correlated; $r = 0.54$, $p < 0.0001$). The weight of a baby is a crude summary of its physique, and the body proportions of the baby may be better described using the ponderal index (birth weight/length^3), with a low ponderal index indicating thinness.[2] This measure of body proportion has been more predictive of later disease than birth weight alone in some studies.[2] There was no significant relation between ponderal index and MHT score. Neither placental weight nor umbilical cord length was significantly related to test score, nor was the birth/placental weight ratio. Social class was significantly correlated with MHT score (male $r = -0.33$, $p < 0.001$; female $r = -0.18$, $p = 0.01$; total $r = -0.26$, $p < 0.001$), but birth weight was not directly correlated with social class ($r = -0.08$, $p = 0.12$). There was no significant change in the results when the data were reanalysed excluding high birth weights, which was done to test for a decrease in score at the highest birth weights (correlation between birth weight and MHT was: all subjects, $r = 0.24$, $p < 0.001$; $n = 449$; excluding births >4200 g, $r = 0.24$, $p < 0.001$; $n = 426$).

MATERNAL CHARACTERISTICS AND MENTAL ABILITY

MHT scores related to maternal characteristics (table 4) show that children born legitimately had higher test scores (mean 36.9 (SD 14.9) *v* 31.0 (SD 15.3); $p < 0.001$). Increasing maternal age was significantly related to higher MHT test scores at age 11 for females only ($r = 0.20$, $p = 0.005$; Spearman's $r = 0.21$, $p = 0.002$; the distribution of maternal age was positively skewed), but not when corrected for legitimacy. The distribution of maternal parity was skewed, and it showed no significant correlation with MHT scores using non-parametric tests (Spearman's $r = -0.07$, $p = 0.13$).

MULTIVARIATE ANALYSES

Multivariate linear regression showed that five predictors contributed significant and partly independent variance to Moray House Test scores: social class, birth weight, age at MHT test, maternal parity, and illegitimacy. Sex, birth length, maternal age, and gestational age were excluded as not contributing independently to the model when the former variables were entered. The five variables account for 15.6% of the variance (adjusted R^2) in the test score age 11. Social class contributes 6.6% (β −0.26), birth weight a further 3.8% (β 0.20), age 2.4% (β 0.16), parity 2.0% (β −0.15), and illegitimacy 1.5% (β 0.12). These contributions are all significant at the $p < 0.001$ level, except illegitimacy ($p = 0.009$). Birth weight therefore accounts for 3.8% of the variance of IQ at age 11, a small, but highly significant, effect size. The relation persists when "low birth weight" babies (<2500 g; $n = 25$) were excluded (contribution to variance: total 15.5%, of which social class 7.9%, birth weight 2.4%, illegitimacy 2.4%, age at MHT test date 2.2%, and parity 1.7%; all $p < 0.002$ except parity $p = 0.007$).

Structural equation modelling was performed to compare the fit of the data with two competing hypotheses. (1) A regression model which posits that social class and birth weight significantly but independently contribute variance to cognitive ability. (2) A mediating variables model in which the effect of social class on cognitive ability at age 11 is mediated (partly or completely) via birth weight (fig 1). The regression model provides the best fit for the data, showing that birth weight, social class and age all contribute variance independently

Table 2 Comparison of groups born in the Royal Maternity and Simpson's Memorial Hospital whose MHT scores were traced with those whose scores were not traced

Variable	MHT scores traced Mean (95% CI)	n*	MHT scores not traced Mean (95% CI)	n	Difference in means (95% CI)	p value‡
Maternal age (y)	27.0 (26.4 to 27.6)	449	25.7 (25.2 to 26.2)	534	1.3 (0.5 to 2.0)	0.001
Parity	2.4 (2.2 to 2.6)	449	2.05 (1.9 to 2.2)	536	0.3 (0.09 to 0.6)	0.009
Gestation (wk)	39.4 (39.1 to 39.7)	339	39.6 (39.4 to 39.8)	432	0.2 (−0.5 to 0.2)	0.35
Days old	3984 (3974 to 3994)	449	3989 (3980 to 3998)	536	5 (−17.2 to 8.7)	0.52
Birth weight† (g)	3317 (3267.5 to 3366.5)	449	3281 (3239.4 to 3322.6)	536	36 (−28.1 to 101.3)	0.26
Birth length (cm)	50.6 (50.3 to 50.9)	428	50.1 (49.9 to 50.3)	503	0.5 (0.14 to 0.86)	0.007
Placental weight (g)	658.8 (632.1 to 685.5)	124	641.6 (618.1 to 665.1)	113	17.2 (−28.5 to 43.1)	0.69
Umbilical cord length (cm)	56.7 (54.6 to 58.8)	121	54.0 (52.2 to 55.8)	109	2.7 (0 to 5.5)	0.06
Ponderal index (kg/m^3)	25.6 (25.2 to 26.0)	428	26.1 (25.8 to 26.4)	503	0.5 (−0.002 to 1.0)	0.07

*Total number of subjects for each variable is not always 449 because of missing data.
†Original data converted to metric: 1 oz = 28 g, 1 inch = 2.5 cm, 1 lb = 453 g.
‡Calculated by paired *t* test on continuous variables.

Table 3 Mean (SD) score in Moray House Test according to birth weight and other variables

	Male				Female				Total				
Variable§	No.	Mean (SD)	Partial r†	p	No.	Mean (SD)	Partial r†	p	No.*	Mean (SD)	r	Partial r†	p
Birth weight (g)													
<2500	9	30.8 (19.3)			16	30.5 (20.1)			25	30.6 (19.4)			
2501–3000	50	35.5 (13.8)			52	33.4 (16.1)			102	34.4 (15.0)			
3001–3500	90	35.6 (14.7)			74	39.4 (14.4)			164	37.3 (14.6)			
3501–4000	62	37.2 (15.3)			53	38.4 (14.1)			115	37.8 (14.7)			
4001–4500	28	44.9 (10.6)			6	43.7 (11.5)			34	44.7 (10.6)			
>4500	7	34.1 (10.5)			2	38.5 (3.5)			9	35.1 (9.4)			
Total	246	36.8 (14.5)	0.23	0.003	203	37.0 (15.4)	0.27	0.002	449	36.9 (14.9)	0.17	0.25	<0.001
Birth length (cm)													
<50	58	35.9 (13.6)			66	34.4 (17.5)			124	35.1 (15.8)			
50–52.4	79	35.7 (14.6)			63	37.5 (14.7)			142	36.5 (14.6)			
>52.5	96	38.0 (14.9)			66	39.0 (13.2)			162	38.4 (14.2)			
Total	233	36.7 (14.4)	0.11	0.014	195	37.0 (15.3)	0.17	0.05	428	36.8 (14.8)	0.11	0.14	0.01
Placental weight (g)													
≤500	13	31.3 (14.0)			5	26.8 (7.2)			18	30.1 (12.4)			
501–600	23	35.6 (13.2)			14	33.7 (20.9)			37	34.9 (16.3)			
>600	38	39.9 (14.2)			30	36.2 (15.0)			68	38.3 (14.6)			
Total	74	37.0 (14.1)	0.18	0.16	49	34.5 (16.3)	0.06	0.72‡	123	36.0 (15.0)	0.15	0.09	0.34
Umbilical cord length (cm)													
<55	41	36.4 (12.7)			24	30.3 (15.2)			65	34.1 (13.9)			
55–62.5	20	38.0 (15.0)			13	37.0 (16.4)			33	37.6 (15.3)			
>62.5	12	37.6 (18.2)			10	38.8 (15.3)			22	38.1 (16.6)			
Total	73	37.0 (14.2)	0.06	0.64	47	33.9 (15.7)	0.28	0.07‡	120	35.8 (14.8)	0.12	0.13	0.17
Ponderal index (kg/m^3)													
<24	70	35.2 (15.9)			82	36.4 (15.9)			152	35.8 (15.9)			
24–25.4	53	37.4 (11.8)			33	37.4 (16.6)			86	37.4 (13.8)			
25.5–27.9	54	36.6 (15.4)			38	38.1 (14.0)			92	37.2 (14.8)			
≥28	56	37.9 (14.0)			42	36.8 (14.6)			98	37.4 (14.2)			
Total	233	36.7 (14.4)	0.01	0.94	195	37.0 (15.3)	0.03	0.71	428	36.8 (14.8)	0.02	0.02	0.69

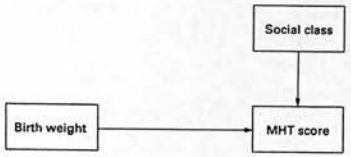
*Total number of subjects for each variable is not 449 because of missing data, number of subjects for partial *r* ranges from 110 to 295 because of missing data and exclusion of extreme outliers: placental weight <180 >1400 g; umbilical cord length >110 cm; gestational age <21 >58 weeks; birth length <37 >62 cm. †Corrected for gestational age, maternal age, parity, social class, and legitimacy. ‡Corrected for gestational age, maternal age, parity, and social class. §Original data converted to metric: 1 oz = 28 g, 1 inch = 2.5 cm, 1 lb = 453 g.

Table 4 Mean (SD) score in Moray House Test according to maternal variables studied

	Male				Female				Total			
	No.	Mean (SD)	r	p	No.	Mean (SD)	r	p	No.*	Mean (SD)	r	p
Gestational age												
<37 weeks	27	34.6 (14.1)			17	39.2 (13.3)			44	36.4 (13.8)		
37–42 weeks	141	38.0 (14.6)			119	37.9 (15.7)			260	38.0 (15.1)		
>42 weeks	21	36.4 (13.2)			14	31.3 (18.1)			35	34.3 (15.3)		
Total	189	37.3 (14.4)	0.09	0.21	150	37.5 (15.7)	0.03	0.69	339	37.4 (15.0)	0.06	0.24
Maternal age												
<25	120	36.8 (14.7)			98	34.5 (14.4)			218	35.7 (14.6)		
25–29	54	37.8 (12.6)			43	35.7 (14.4)			97	36.9 (13.4)		
>29	72	36.2 (15.7)			62	41.9 (16.5)			134	38.8 (16.3)		
Total	246	36.8 (14.5)	0.01	0.90	203	37.0 (15.4)	0.20	0.005	449	36.9 (14.9)	0.10	0.038†
Parity												
0	114	38.2 (15.4)			109	37.1 (15.4)			223	37.6 (15.4)		
1–2	79	37.1 (14.1)			60	38.3 (13.6)			139	37.6 (13.9)		
3–4	22	33.5 (10.6)			19	32.8 (17.6)			41	33.2 (14.1)		
>4	31	33.6 (14.4)			15	36.7 (19.3)			46	34.6 (16.0)		
Total	246	36.8 (14.5)	−0.14	0.03	203	37.0 (15.4)	−0.04	0.58	449	36.9 (14.9)	−0.07‡	0.13
Legitimacy												
Legitimate	204	38.4 (14.2)			174	37.6 (15.1)			378	38.0 (14.6)		
Illegitimate	42	29.5 (14.2)			29	33.4 (16.7)			71	31.1 (15.3)		0.001§

*Total number of subjects for each variable is not 449 because of missing data and exclusion of extreme outliers: gestational age <21 >58 weeks.
†Spearman's *r* male 0.04, p 0.52; female 0.21, p 0.002; total 0.12, p 0.009.
‡Spearman's *r*.
§*t* test.

Regression model



Mediating model

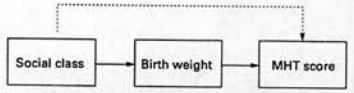


Figure 1 Two competing models of the associations among birth weight, social class, and MHT scores. The regression model hypothesises independent effects of parental social class and birth weight on IQ. The mediating model hypothesises that birth weight acts as a partial or total mediator of the inference of parental social class on later IQ score.

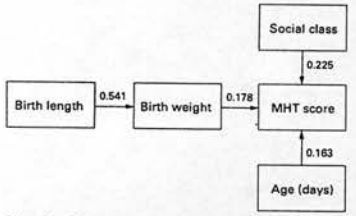


Figure 2 Best fitting model of the associations among birth weight, parental social class, and IQ at age 11 years. Model fitting was performed using EQS.[29] Note that parental social class, birth weight, and age at test date have independent influences on age 11 IQ. The effect of birth length is entirely mediated by birth weight. The numbers adjacent to arrows are parameter weights estimated by EQS; squaring them gives the variance shared by adjacent variables. This model has comprehensively good fit statistics.

to Moray House Test score age 11 (fig 2). The model shown in fig 2 has comprehensively good fit statistics, as follows: the average off diagonal absolute standardised residuals was 0.038 (the model accounts for most of the covariance among the variables shown); the model χ^2 was 8.86, df = 6, p = 0.18 (non-significant χ^2 values indicate well fitting models); Bentler–Bonett normed fit index = 0.953, Bentler–Bonett non-normed fit index = 0.973, comparative fit index = 0.984 (values above 0.9 indicate well fitting models); all parameter weights in the model were significant; the Wald test found no parameters that might be dropped and the Lagrange multiplier test found no additional parameters that might improve the model (neither a more nor less economical model fits better than the one shown). Models in which birth weight acted as a mediator of social class had poor fit statistics (details available from the authors).

Discussion

In this cohort social class, birth weight, age, pregnancy number, and legitimacy of birth contribute some non-overlapping predictive power to cognitive function age 11 years. Birth weight and social class explain the largest amount of the variance, are not significantly correlated, and each make an independent contribution to IQ at age 11. Birth weight explains 3.8% of the variance in IQ at age 11, and social class accounts for 6.6% of the variance. These are small but significant effect sizes, and it is clear how large a proportion of the variance remains unexplained by these factors. Importantly, the relations in this cohort exist across the normal range of birth weight and mental ability. The reduced cognitive test scores at high birth weights seen in previous studies were not statistically significant here. Our findings agree with those of Seidman and colleagues,[10] Sorenson and colleagues,[9] and Richards and colleagues[8] that birth weight and social class can explain a proportion of the variance in later psychometric intelligence. Martyn and colleagues[11] found this relation to be not statistically significant, but used an indirect estimate of early life intelligence.

The fact that the relation between birth weight and childhood mental ability is observed over distinct historical periods implies that it is robust, making it tenable that mechanisms have remained unchanged over time. Data from historical studies can thus provide valuable information about early life predictors of disease, which are still relevant today.[2 3 14] Moreover, a major strength of this cohort is the ability to compare performance on cognitive testing with almost the entire Scottish population born in the same year. This allows us to put the scores for the sample in the context of the whole 1921 born population. The subjects were both male and female, and particularly well characterised, allowing correction for gestational age, placental weight, and social factors. The well defined, narrow cultural epoch minimised variation in external, cohort specific influences on cognitive development.

As in other cohort series, however, there is significant loss to follow up. The main difficulty was in ascertaining the correct test record for illegitimate births, probably because the child's name was changed by marriage or adoption (formal and informal). This may explain why the test scores that were traced were significantly better than the general population, as illegitimate children were likely to be brought up in relatively deprived environments, and thus perform less well, but they are, nonetheless, comparable with the entire Scottish population tested in 1932.

The suggestion that birth weight is merely a marker of social deprivation is not supported here. There is no direct correlation between birth weight and social class, replicating the result from previous studies of the programming hypothesis,[21] and modelling confirmed that the effect of social class was not mediated by birth weight. Having shown independent associations among birth weight, social class, and childhood mental ability, it is now important to investigate potential mechanisms. This study did not address these. Birth weight and social class are crude markers of fetal development and the environment in which a child develops, and the underlying mechanism of their influence on childhood intelligence is unclear. The programming hypothesis has suggested that shortage of specific nutrients at critical stages of development may be responsible for the relation between birth weight and mental ability,[5] and the timing of these insults on the developing brain is likely to be important.[4] Neurochemical influences such as insulin like growth factors have also been implicated.[8] Ongoing deprivation throughout life, for which social class at birth is a poor approximation,[14] plays a significant role in determining outcome.[12]

The relative importance of different early life influences might have changed since the 1920s. This could affect the relation between early life factors and later intelligence in many ways. For example, high infant mortality means that the effect of selective influences on survival was greater. In 1921, 115 per 1000 children died by the age of 10[22] (in 2000 the mortality rate was less than 6 per 1000[23]), and a large proportion of these might have had relatively low birth weights. This would tend to decrease the strength of any relation between birth weight and mental ability. Furthermore, the study population was born in hospital, at a time when the majority of births occurred at home. A large proportion of these births was illegitimate and, although this explains some of the differences between the sample and the population, it does not explain the relations seen within the sample itself. The proportion of births registered to unmarried mothers in Scotland in 1921 was 7.1%,[22] compared with 42.6% in 2000.[23] Seven per cent, however, were registered by the mother alone, implying a similar proportion of unsupported single mothers as in 1921, although the social impact of an illegitimate birth is likely to have changed considerably. Furthermore, the prevalence of breast feeding, an important factor in physical and mental development,[24] has fallen dramatically in the past 79 years, from 80% to 55% at 10 days, and from 50% to 19% at 6 months.[14 23] There continues to be concern about children's nutrition, and the wider environment in which many children are raised. General standards of housing have improved, with less overcrowding, but many children are raised in areas of deprivation with poor housing. The degree of social inequality in Scotland today means that postnatal influences may be more variable across communities than across time.[25]

Social class has been seen as a broad indicator for a range of socioeconomic influences and, therefore, in previous studies, controlling for social class was thought to control for confounding by other social factors.[14] A recent study that also examined Scottish children in 1921, however, showed that social class derived from paternal occupation may not adequately describe the environmental influences on the developing child.[14] Furthermore, variation in income is greater within the bands of social class than between them.[26 26] Therefore, the contribution of social class to mental ability is likely to have been underestimated, partly also because of the narrow range of social class in this sample. The wider socioeconomic environment[27] may therefore explain a proportion of the unexplained variance in mental ability scores. Other influences include genetic factors, which account for 40–70% of the variance in mental test scores.[27] Also, birth weight is a very crude marker of fetal growth and nutrition, and other measures of intrauterine influences such as head size may be important,[11] but were not available to us.

Although health care today differs significantly from the period studied, these historical data are important for future studies, not least because they show that the association between early life factors and childhood mental ability holds across distinct cohorts. Moreover, the historical nature of this data provides an opportunity to study this cohort in detail now, in old age, to relate their childhood data to their current health and cognition, at a time in their lives when these are critical.

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Commentary

The hypothesis that nutritional factors may programme the fetus and influence the risk of subsequent death or morbidity is of considerable public health significance. There is a wide range and variety of adult disability that may be attributable to fetal and early child development.[1] The past quarter century has seen important developments in the care of the neonate with a corresponding improvement in survival of ever smaller infants. This has generated questions on the quality of survival, not only in relation to overt clinical disability but also in more subtle and subclinical deficits of cognitive and motor function. To be able to obviate or ameliorate these deficits, the differential contribution of intrauterine growth restriction as a marker of fetal malnutrition, preterm delivery, and social and other environmental factors acting pre- or postnatally, is needed. Difficulty in disentangling the relative contribution made to cognitive and other deficits arises because these several influences are highly correlated and because cause and effect cannot be assumed.

Several geographically defined population cohort studies, examining cognitive development in relation to birth weight, have focused on a comparison of low and normal birth weight infants and found that the low birth weight infants do not perform as well as their normal birth weight controls.[2–4] Within the low birth weight infant group, differential effects of small for gestational age, preterm delivery, and social factors have also been observed in relation to cognitive function.[5] The association of birth weight and later cognitive function among infants of all birth weights is not clear cut. One study found no significant association,[6] while another concluded that fetal growth may influence subsequent adult cognitive function.[7]

The study reported by Shenkin *et al* uses a historical cohort born in 1921 and found independent associations of birth weight and social class with cognitive function assessed when the cohort was aged 11 years. Although birth weight and social class had independent effects in a multiple regression, a statistical model of birth weight acting as a mediator of social class had a poor fit. The authors have done well to link successfully almost 50% of the birth and mental test result records as so long a time has elapsed. Nevertheless, the problem of non-response bias must be considered in assessing the validity of the observations.

The fundamental question all these studies endeavour to answer is whether the cerebral impairment is prenatal or postnatal in timing and whether environmental factors, of which social class is a surrogate measure, have an important influence. Possible preventive and remedial measures will be dependent on the answers to these questions. One caveat that should be borne in mind, concerns the tests that are used to assess cognitive function. What do these tests actually measure? Ideally they measure innate mental ability, whatever that is, at a point in time. However, in spite of efforts to design tests that are "culture free", none meet this criterion, whether it is the Moray House Test as used by the authors in this study, the Wechsler Intelligence Scale for Children, the Goodenough Draw-a-Man test, or any other measure of cognitive function. Social class differences in cognitive performance tests are culture dependent and it should not be inferred that these are attributable to differences in intellectual capacity or to cerebral impairment. For example, children who have limited access to pencil and paper are likely to perform less well on the draw-a-man test than those with better resources, irrespective of their cognitive ability. The social class cultural effect on tests of cognitive ability may overshadow the social class effect mediated through birth weight.

Shenkin *et al* have provided valuable data that will inform the debate in this important field but the debate is likely to continue for years to come.

EMERITUS PROFESSOR P O D PHARAOH
FSID Unit of Perinatal and Paediatric Epidemiology, Dept of Public Health, Muspratt Building, Liverpool L69 3GB, UK

1 Barker DJP, ed. *Fetal and infant origins of adult disease.* London: BMJ Publications, 1992.

2 Lloyd BW, Wheldall K, Perks D. Controlled study of intelligence and school performance of very low-birth-weight children from a defined geographical area. *Dev Med Child Neurol* 1988;30:36–42.
3 Abel Smith AE, Knight-Jones EB. The abilities of very low-birthweight children and their classroom controls. *Dev Med Child Neurol* 1990;32:560–601.
4 Pharoah POD, Stevenson CJ, Cooke RWI, Stevenson RJ. Clinical and subclinical deficits at 8 years in a geographically defined cohort of low birthweight infants. *Arch Dis Child* 1994;70:264–70.
5 Hutton JL, Pharoah POD, Cooke RWI, Stevenson RC. Differential effects of preterm birth and small for gestational age on cognitive and motor development. *Arch Dis Child Fetal Neonatal Ed* 1997;76:F75–F81.
6 Martyn CN, Gale CR, Sayer AA, Fall C. Growth in utero and cognitive function in adult life: follow up study of people born between 1920 and 1943. *BMJ* 1966;312: 1393–6.
7 Sorensen HT, Sabroe S, Olsen J, *et al.* Birth weight and cognitive function in young adult life: historical cohort study. *BMJ* 1997;315:401–3.

9.2 Preliminary practice test from Scottish Mental Survey 1932

PRELIMINARY PRACTICE TEST

Read each question carefully, and then answer it in the bracket, or by underlining, or as it tells you

The alphabet is printed here to help you:

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

BEGIN HERE:

(1) Do you understand that you must do your best and not ask questions?
If so, write B .....( )

(2) Write the three letters between A and E and cross out the middle one.....( )

(3) Finger is to hand as toe is to what? The answer is one of the five words in the bracket.

Underline the right word ..... (foot, knee, arm, shoe, nail)

You have nothing to write, only UNDERLINE what you think is the right answer.

(4) Man is to clothes as what is to fur? .....(coat, animal, bird, skin, cloth)

(5) Three boys are Scottish, Irish, and English. The English boy is taller than the Irish, but the Scot is tallest of all.

Which is the shortest?.....(English, Irish, Scottish)

(6) Underline the ONE of the four answers to this statement which seems to you to be correct:

Bathbrick is used for (making baths, building houses, cleaning, cooking).

(7) If H comes before K write **X**, unless S comes before Q, in which case write **Z** .....( )

(8) Fill in the missing figure in this addition sum and write it in the bracket as well:
.....( )

	7	2	.	3
	4	1	6	2
1	1	4	5	5

9.3 Information, consent and data collection forms (birth, cognitive, physical data)

1. Information sheet
2. Consent form
3. Summary data collection form
   - medical, social, cognitive and physical data
4. Summary data collection form
   - ABPI, neurological and childhood social data
5. Data collection form
   - current and childhood socioeconomic data
6. Data collection form
   - medical history
7. Data collection form
   - ABPI and neurological examination
8. Data collection form
   - Carotid ultrasound results

The Simpson's Study: lifetime influences on cognition
Information Sheet

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

This study is based on the discovery of birth records from the old 'Simpson's' hospital (Royal Maternity and Simpson Memorial Hospital), Lauriston Place, Edinburgh, Lying-in Hospital and Elsie Inglis, from the 1920s. We know that the condition of babies when they are born, in particular how much they weigh, is an important influence on health in later life. We do not know, however, whether birth weight might be one of the things that affects how your 'thinking skills' (cognition) change over your lifetime. As your birth records include information on birth weight, you can help us to answer this question.

Do I have to take part?

You have been sent this information because you replied to an advert, poster or leaflet. This in no way obliges you to take part in the study. It is up to you to decide whether or not to take part. If you do decide to take part, you will be given this information sheet to keep and asked to sign a consent form. You would still be free to withdraw at any time and without giving a reason. This will not affect the care you receive from the hospital or your GP.

What will happen to me if I take part?

If you agree to take part in the study we will **ask you** about your early life, education, work and health. We will also **measure** some simple things like how fast you can walk a short distance, your blood pressure, vision, how fast you can breathe out, and check your reflexes. To measure how your memory and other mental abilities are just now, we will ask you to do some simple mental tests.

We would also like to **take some blood** for some simple tests, e.g. blood count, cholesterol, and some to store so that it can be tested for different genes later on. The blood stored for gene testing will be kept completely anonymous as these tests are of no importance for your health as an individual. However, these gene tests are important for us to understand why some people are more likely than others to have problems with their memory.

Asking you questions and the tests will take around $3^1/_2$ hours, including time for tea breaks. These would normally be done at the purpose built Wellcome Trust Clinical Research Facility, at the Western General Hospital.
We would also like to arrange special **scans** to see if small changes that happen in the blood vessels and the brain relate to birth weight and difficulties with delivery. One is an ultrasound scan of the blood vessels in your neck, which is totally painless. The other is a very detailed brain scan (MRI).

As this uses strong magnets, not X-rays, you would not be able to have the scan if you have any metal in your body, e.g. cardiac pacemaker, some heart valves, aneurysm clips or metal pieces in your eyes. The ultrasound scan takes around 15 minutes, the MRI around 35 minutes. These will be done at the Western General Hospital, normally on a separate day than the other tests, and this whole visit will take 1-1$^{1}/_{2}$ hours.

What are the possible disadvantages of taking part?

A few people experience mild claustrophobia once inside the scanner, in which case the scan would be stopped immediately. The scanner also makes a loud rattling noise, and you will therefore be given earplugs to wear. There are no known side-effects from the scans themselves. There is a small chance that the tests may show up an unusual result, although you feel well. For example, your blood pressure might be high, a blood test might be abnormal, or a small stroke may show up on the scan. We would discuss this result with your GP, and they would explain the results to you, and arrange any further tests if necessary.

What are the possible advantages of taking part?

This study is 'non-therapeutic research', and there is no direct clinical benefit to you. We do hope, however, that the information we get from this study will help us to understand whether what happens to us in early life, and even before we are born, is important for our thinking skills as we get older. This may help us to target advice in the future to help prevent some of the difficulties people experience as they get older.

Will my taking part in the study be kept confidential?

All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the University will have your name and address removed so that you cannot be recognised from it.
Your GP will be informed that you are taking part in this study, and will get a copy of the results.

What happens to the results of the research study?

We will keep you up-to-date with our findings in a newsletter. We hope the results will be published in scientific journals in the next 1-3 years. You will not be identifiable in any publication.

Who is organising and funding the research?

The research is a joint project between the departments of Psychology and Geriatric Medicine at the University of Edinburgh. Dr Shenkin, who will contact you and carry out the tests, was funded for this project by a Clinical Training Fellowship from the Medical Research Council. Chest, Heart and Stroke, Scotland are funding the brain scans.

Contact for further information

If you would like to discuss the project,
or have any queries, please do not hesitate to contact:
Dr Susan Shenkin
University of Edinburgh
7 George Square, Edinburgh
Tel: 0131 651 1686

If you would like **independent advice** about the study, from a doctor who is aware of the study but not directly involved in the research, please contact:
Dr Elizabeth MacDonald
Department of Geriatric Medicine
Royal Victoria Hospital, Edinburgh
Tel: 0131 537 5000

Thank you very much for considering taking part in this study.

Study Number: E00029A
Subject identification number:

Consent form

Title of Project: **The Simpson's Study: lifetime influences on cognition**

Researcher: Dr Susan Shenkin
University of Edinburgh
Department of Psychology
7 George Square
Edinburgh
EH8 9JZ

Please initial box

1. I confirm that I have read and understood the information sheet for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that sections of my medical notes may be looked at by researchers where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐

4. I give permission for my name and address to be retained on file for this study. I understand that this information will be kept confidential and not made available to any other party. ☐

5. I agree to take part in the above study. ☐

Name of subject	Date	Signature
Researcher	Date	Signature

1. STUDYNO
2. ATTEND
3. ATTEND2
4. AT HOME
5. WHOTEST
6. ADDCOMM
7. CVHIST
8. CRVHIST
9. NEOPLAS
10. HIBP
11. DIAB
12. THYROID
13. DEMENT
14. OTHVASC
15. OTHDIS
16. COMNTDIS

17. ONMEDS
18. DRUG1-DRUG8
19. DATETEST
20. NEWADD1
21. NEWADD2
22. NEWCITY
23. NEWPCODE
24. MAIDN
25. PLBORN
26. SCHLATT
27. YRSEDUC
28. OCC
29. SOCCL
30. LIVEALN
31. RESDNC
32. HMHLP
33. SMOKER
34. AGESTART
35. AGESTP
36. NOPDAY
37. ALCPW
38. HADA
39. HADD
40. MMSE
41. MEMA
42. MEMB
43. MHT
44. MEMDELA
45. MEMDELB
46. DEMIS
47. HEIGHT
48. WTKG
49. SITSTND
50. TEETH
51. BPSIT
52. BPSTAND

53. FEV1, FEV1, FEV1

54. FVC, FVC, FVC
55. FER, FER, FER

56. PEF, PEF, PEF
55. GRPSTR
57. VISR_UN
58. VISL_U
59. VISR_C
60. VISL_C
62. 6MTIME
63. ECG?
64. GENETIC?
65. BL1, BL2, BL3?
66. TOWNSEND
67. NART
68. RAVENS
69. VFC, VFF, VFL, VFTOT

1. STUDY NO.
2. CN
3. DATE TEST
4. WHERE TEST
5. BP
6. R BRACHIAL
7. L BRACHIAL
8. R BRUIT
9. L BRUIT
10. R PT
11. R DP
12. L PT
13. L DP
14. RESULT
15. ABPI
16. IC SYMPTOMS
17. GAIT
18. FIELDS
19. FIELDS CODE
20. EYE MVMNT
21. EYE MVMNT CODE
22. NYSTAGMUS
23. DIPLOPIA
24. FAC SENSN
25. FAC WK UPP
26. FAC WK LOW
27. HEARING
28. COUGH
29. SWALLOW
30. AAH
31. TONGUE MVMT
32. DYSPHASIA
33. DYSARTHIA
34. TONE RUL
35. TONE LUL
36. TONE RLL
37. TONE LLL
38. POWER RUL
39. POWER LUL
40. POWER RLL
41. POWER LLL
42. REFL RB
43. REFL RS
44. REFL RT
45. REFL LB
46. REFL LS
47. REFL LT
48. REFL RK
49. REFL RA
50. REFL LK
51. REFL LA
52. R PL
53. L PL
54. COORD RUL
55. COORD LUL
56. COORD RLL
57. COORDN LLL
58. FATHER OCC
59. MOTHER OCC
60. ADDR 11
61. NO. ROOMS
62. PEOPLE
63. TOILET
64. SHARE TOILET
65. FH
66. BIRTH WEIGHT
67. MDIEDAGE
68. MDIEDCAUSE
69. FDIEDAGE
70. FDIEDCAUSE
71. NOTES

Simpson's Study Subject Data

Date ……..……

Demography

Maiden Name…….. Place of Birth……..

Birth weight……

Schools attended ……

Years of full-time education……..…

Highest qualification achieved……..…

Occupation……

…….…….. SOC……..

Father's occupation…… Mother's occupation…….

Lives alone YES/NO Home Help (times per week)……

Residence Own home / Rented accom (council/ private)/ Residential Home / Nursing Home / Hospital

Address **age 11**……..…….

Rooms in house ……. People in house……

Toilet IN / OUTDOOR No.of people sharing toilet facilities…

Smoker Yes/ No/ Ex Age started…….. Age stopped……..No/day……

Alcohol (units/week)……..

Family history CVD/CHD……...

Mother died age…… cause ……Father died age…….. cause …..…….....

GP name and address……

Simpson' Study Health Information

History of disease

Cardiovascular	YES / NO
Cerebrovascular	YES / NO
Neoplasia	YES / NO
Hypertension	YES / NO
Diabetes	YES / NO
Thyroid disorder	YES / NO
Dementia	YES / NO
Other vascular disease	YES / NO
Other disease	YES / NO

Comments .....

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On medication YES / NO

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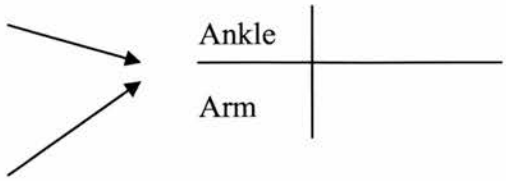
Simpson's Study ABPI/Neuro

ABPI

	Left	Right	
Posterior tibial			LOWEST
Dorsalis pedis			
Brachial			HIGHER



Circle lowest ankle and higher arm reading

IC symptoms..... ABPI= ☐.☐☐

Neurology

1. Gait .....
2. Fields .....
3. Eye movement .....
4. Nystagmus .....
5. Diplopia .....
6. Facial sensation .....
7. Facial weakness upper .....
8. Facial weakness lower .....
9. Hearing .....
10. Cough .....
11. Swallow .....
12. Aah .....
13. Tongue movement .....
14. Dysphasia .....
15. Dysarthria .....
16. Carotid Bruit R .....L.....

17. Tone

RUL	LUL
RLL	LLL

18. Power

RUL	LUL
RLL	LLL

19. Reflexes

RB	RS	RT
RK	RA	RP
LB	LS	LT
LK	LA	LP

20. Coordination

RUL	LUL
RLL	LLL

Simpson's Study
Carotid ultrasound results

Subject name ..... Date.....
Address .....
Date of Birth ..... CN .....

CAROTID ARTERY

Maximum stenosis (%)	LEFT	RIGHT
0-20	☐	☐
21-40	☐	☐
41-60	☐	☐
61-80	☐	☐
81-99	☐	☐
100	☐	☐
Site		
CCA	☐	☐
ICA	☐	☐

Other
.....

Comments .....

VERTEBRAL ARTERY

	Yes ☐ No ☐	Yes ☐ No ☐
Normal?		

If no, comments.....

INTIMA MEDIA THICKNESS	☐.☐	☐.☐
INTIMA ADVENTITIA THICKNESS	☐.☐	☐.☐

Operator.....

9.4 Apolipoprotein E genotyping

Genotyping for *APOE* was done at the Wellcome Trust Clinical Research Facility Genetics Core. After extraction the samples were quantified using the RNase P assay from Applied Biosystems. A short description of the DNA extraction & quantification provided by staff at the Genetics Core follows.

DNA extraction from whole blood using the Nucleon BACC3 protocol

The first stage is the *cell preparation* from whole blood which is achieved by adding blood to 50ml tube and adding 4x Reagent A (rotary mix for 4 mins, Spin for 5 and discard supernatent). The second stage is *cell lysis* which is achieved by adding 2 ml of reagent B and vortexing. The third stage is *deproteinisation* which occurs by the addition of 500ul sodium perchlorate and inverting 7 times. The next stage is the *extraction* stage achieved by first adding 2 ml of chloroform and inverting 7 times and then adding the nucleon resin to separate the phases and spin down for 3 mins. In the next stage, *DNA precipitation,* the upper phase is transferred to another 15ml tube, 2 volumes of 100% ethanol added, and inverted several times until the DNA strand appears. The DNA is then removed using a glass pasteuer pipette washed in 70% ethanol and put into 1ml tube of TE, which is put onto a rotary wheel for 1 week to allow it to go into solution.

DNA sample quantification using RNase P kit.

The reaction mix for PCR is prepared from the 20x probe/primer mix from the TaqMan RNaseP Control Reagents kit comprising : 2x Abgene Absolute QPCR ROX mix (5µl), 20x Probe/Primer Mix (0.5µl) and dH_2O (2.5µl). 8µl of reaction mix is aliquotted to each well to be used. The following dilutions of the Human Genomic Control DNA are made: 0.5ng/µl, 1ng/µl, 2ng/µl, 5ng/µl and 10ng/µl. These will be used as the standards for the standard curve. 2µl of each are aliqotted into a 384 well plate in duplicate. 1/100 dilution is made of all samples to be quantified. 2µl of each diluted sample is aliquotted into the same 384 well plate. The plate is spun down briefly in 2-16 centrifuge (4000 rpm for 15 seconds), and run in the 7900HT Sequencing Detection System.

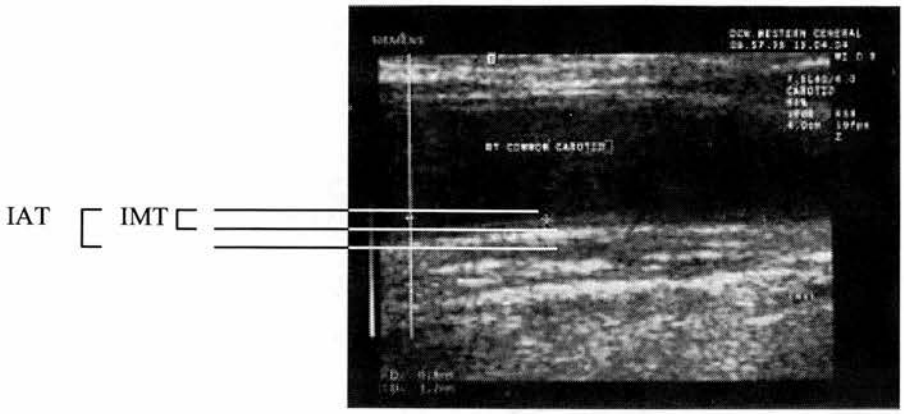
9.5 Carotid artery ultrasonography methodology

Carotid ultrasound was performed by Mrs Elizabeth Eadie and Professor Joanna Wardlaw using a 5-7MHz probes operating in colour Doppler mode (Acuson 128xp 10 v until summer 2002, Siemens Elegra subseqently).

A longitudinal examination of the carotid arteries was performed using a standard procedure (Zwiebel, 1992) from the most inferior visible part at the base of the neck to high up underneath the mandible. The common, internal and external carotid arteries were examined individually. Representative peak velocity and end diastolic velocity readings were recorded from each vessel. Each vessel was examined for the presence of atheromatous stenosis. If atheroma was present the degree of stenosis was measured by measuring the residual lumen at the point of maximum stenosis and then the original diameter of the artery, which is visible on ultrasound. This equates to the European Carotid Surgery Trial method of measuring stenosis angiographically and is identical to the method that uses the common carotid artery as a denominator. The internal carotid peak systolic velocity was measured at the point of maximum stenosis, and compared to standard tables (Zwiebel, 1992) to determine the degree of stenosis. An estimate of the degree of maximal stenosis (in 20% increments), and the site, was recorded. The vertebral arteries were examined: if they appeared normal this was noted, and if not the reason was recorded.

Intima media thickness (IMT) and intima adventitia thickness (IAT) were measured on a longitudinal, two dimensional image of the distal common carotid artery (Pignoli et al., 1986; Wendelhag et al., 1991; Kanters et al., 1997). When an optimal longitudinal image was obtained it was frozen on screen, and the IMT and IAT measured in the far wall (Figure 9.1).

Figure 9.1 B-mode ultrasound image of distal common carotid artery with IMT and IAT marked.



9.6 Structural magnetic resonance imaging

9.6.1 Structural imaging protocol

Brain imaging was performed in a GE Signa LX 1.5T scanner (General Electric, Milwaukee, WI, USA). The participant was positioned supine in the scanner and given ear plugs and/or defenders. A transmit and receive head coil was used (GE). The T2FSE, FLAIR and T2* Gradient echo axial sequences were prescribed with an angulation through the anterior commisure/posterior commisure line.

The Diffusion tensor imaging (DTI) sequences were obtained in the axial plane without angulation. The volumetric sequence was obtained in a coronal plane angled at 90 degrees to the hippocampus.

Structural image acquisition followed a 3-plane localiser and consisted of

(1) sagittal T1-weighted spin-echo (TR 450, TE 8, slice thickness 5mm, inter-slice gap 1.5mm, FOV 24 cm, matrix 256 x 224)

(2) axial T2-weighted fast spin-echo (FSE) (TR 6300, TE 102, slice thickness 5mm, inter-slice gap 1.5mm, FOV 24 cm, matrix 256 x 256)

(3) axial fluid attenuated inversion recovery (FLAIR) (TR 9000, TE 140, TI 2200, slice thickness 5mm, inter-slice gap 1.5mm, FOV 24 cm, matrix 256 x 224)

(4) axial T2* gradient echo (TE 15, TR 625, slice thickness 5mm, inter-slice gap 1.5mm, FOV 24 cm, matrix 256 x 192), and

(5) three-dimensional fast spoiled gradient echo T1 weighted volume sequence (inversion recovery prepared) with whole brain coverage (TI 400, flip angle 20°, slice thickness 1.7mm (no interslice gap), FOV 24cm, matrix 256 x 256).

The scan duration was approximately 40 minutes.

9.6.2 Volumetric image analysis

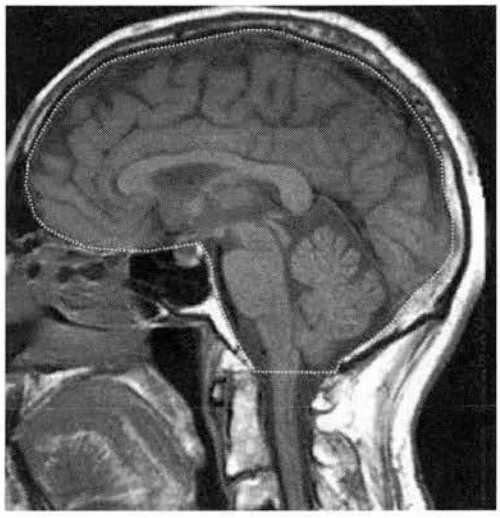
Analysis of volumes was performed by Ms Carly Rivers who was blind to all data collected in the study, and to the hypotheses of the study.

Images from the MRI scanner were transferred onto a Sun workstation and processed into an Analyze™ (Mayo Clinic, Rochester, MN) readable format. All analyses were performed using Analyze™ software. An intensity threshold separating the brain from the meninges was imposed for semi-automated analysis.

Intracranial area (ICA)

This was measured in the midline sagittal slice of the sagittal localiser by manually tracing round the inner table of the cranial vault, along the superior surface of the floor of the frontal fossa and across the pituitary fossa to the dorsum sella. Tracing continued down the posterior surface of the clivus and completed by a line joining the anterior and posterior rims of the foramen magnum. Dura mater and venous sinuses were included, air-filled sinuses and pituitary were excluded (Figure 9.2).

Figure 9.2 Definition of intracranial area



Corpus callosum area

This was derived by manually traced around the edges of the corpus callosum (Figure 9.3).

Figure 9.3 Definition of corpus callosum

Whole brain volume

Brain volumes were measured from the 3 directional 128-slice scan at 90° to hippocampus. The brain was thresholded to eliminate the maximum of 'non-brain' tissue (bone, meninges) before performing the analysis. The whole brain volume includes all brain tissue, with a limit imposed in a horizontal line across the bottom-most part of cerebellum as posterior limit.

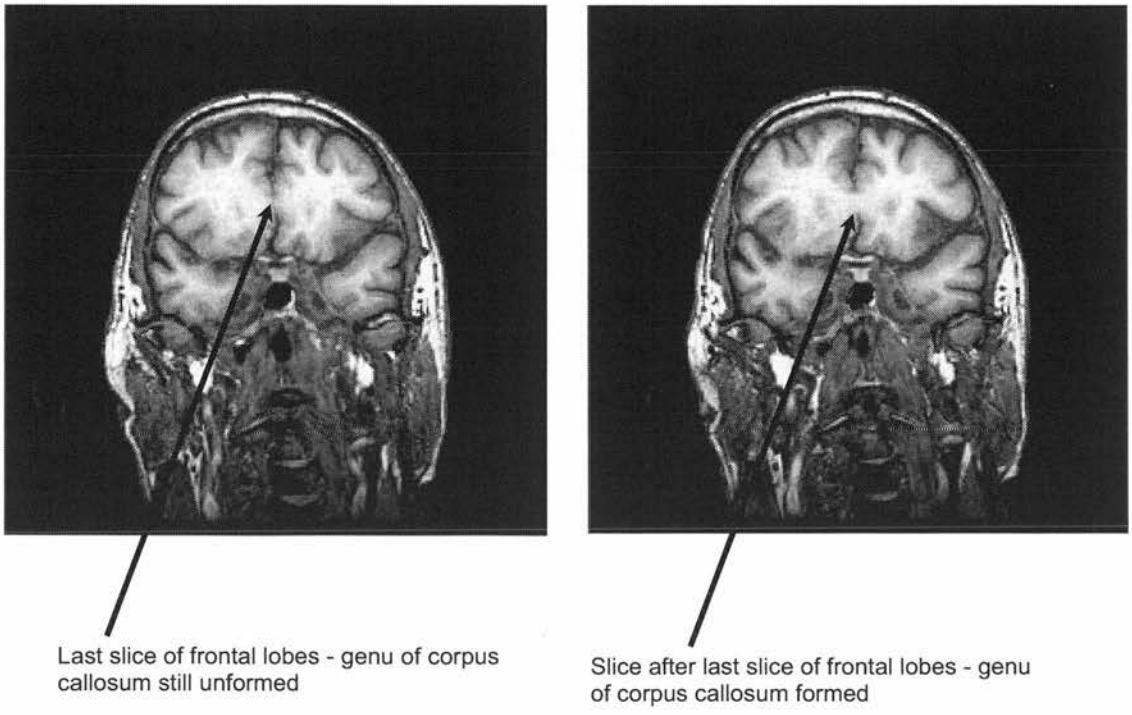
Ventricular volume

The volume of the lateral, 3rd and 4th ventricles was included.

Frontal lobe volume

Frontal lobe volumes were measured from the slice in which the frontal pole could be distinguished from the meninges. Measurements were made using automated methods with manual tracing to separate the lobes through the inter-hemispheric fissure. Frontal lobes were split into left and right hemispheres and included from the pole of the frontal lobes to the slice immediately preceding the genu of the corpus callosum (where the corpus callosum is fully formed) (Figure 9.4).

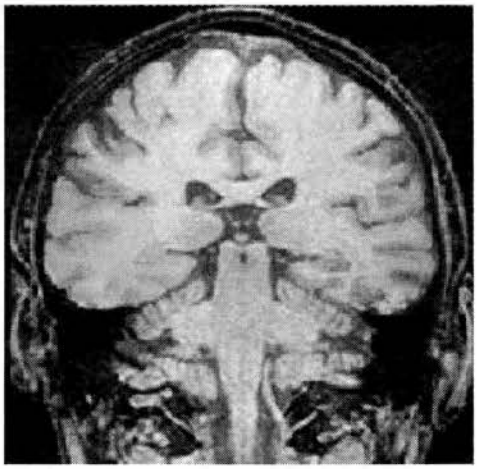
Figure 9.4 Definition of frontal lobe



Temporal lobe volume

Temporal lobes (right and left) were measured separately including tissue from the temporal poles to the last slice in which the fibres of the crux of the fornix appears distinct from the hippocampus and the walls of the lateral ventricles (Figure 9.5).

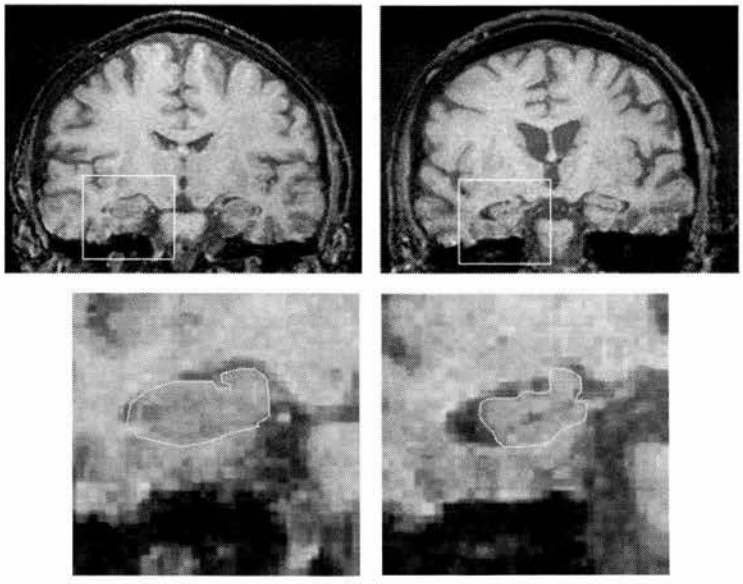
Figure 9.5 Definition of temporal lobe



Amygdalo-hippocampal complex (AHC)

This was defined as subiculum, hippocampus proper and dentate gyrus with the alveus and fimbria. The AHC was measured bilaterally using manual tracing from the first slice where the temporal stem is fully formed until the last slice of temporal lobes, where the crus fornicis appeared distinctly (Figure 9.6).

Figure 9.6 Definition of amygdalo-hippocampal complex



Intrarater reliability

In a training period, brain volume analyses were rehearsed until consistent results were obtained. Repeat volumetric analyses showed errors of < 1%.

The imaging analysis protocol has been previously reported and validated (MacLullich et al., 2002; Whalley et al., 1999; Whalley & Deary, 2001).

9.6.3 White matter lesions analysis

Coding of white matter lesions (WML) was performed by Professor Joanna M Wardlaw who was blind to all data collected in the study. The final 20 scans were coded by Professor Jonathan Best and were checked by Professor Wardlaw to ensure consistency.

Each scan was coded on several ordinal scales detailed below.

(1) **Atrophy** (a) ventricles (0-3) and (b) sulci (0-3)

(2) **Wahlund** (a) CSF (estimates size of subarachnoid spaces and vertricular size) (1-3) (b) WML (considers periventricular hyperintensities (PVH) and deep white matter hyperintensities (DWMH) together) (1-3) (Wahlund, Almkvist, Basun, & Julin, 1996)

(3) **Longstreth** considers PVH and DWMH together (0-8) (Longstreth, Jr. et al., 1996)

(4) **van Swieten** considers PVH and DWMH together (a) anterior (0-2) and (b) posterior (0-2) (van Swieten, Hijdra, Koudstaal, & van Gijn, 1990)

(5) **Breteler** PVH only (0-2) (Breteler et al., 1994)

(6) **Fazekas** (a) PVH (0-3) (b) DWMH (0-3) (Fazekas et al., 1987)

(7) **Shimada** PVH only (1-4) (Shimada, Kawamoto, Matsubayashi, & Ozawa, 1990)

(8) **Mirsen** (a) PVH absent or present (b) DWMH (0-4) (Mirsen et al., 1991)

(9) **Gradient echo** microbleed (1, 2 , 3 or more), basal ganglia smudge, other haemorrhage or primary intracranial haemorrhage

(10) **Small punctate lesions** (a) hippocampus (b) basal ganglia (c) centrum semiovale (0-4)

(11) **ARWMC** (a) WML (0-3) (b) basal ganglia lesions (0-3) (Wahlund et al., 2001)

Descriptive statistics for these scales are shown in Table 9.1.

Table 9.1 Descriptive statistics for various white matter lesion scores (n = 110)

Scale	Med	IQ range	Min	Max	Possible score
Ventricle atrophy	2	1, 2	0	3	0-3
Sulcal atrophy	1	1, 2	0	3	0-3
Wahlund	2	1.5, 2	1	3	1-3
- Size of CSF spaces					
- WML (PVH+DWMH)	2	1.5, 2	0	3	1-3
Longstreth (PVH+DWMH)	2	2, 3	1	8	0-8
van Swieten anterior WM	1	0, 1	0	2	0-2
van Swieten posterior WM	1	1, 1	0	2	0-2
Breteler PVH	1	0, 1	0	2	0-2
Fazekas PVH	1	1, 2	1	3	0-3
Fazekas DWMH	1	1, 1	0	3	0-3
Shimada PVH	2	2, 3	0	4	1-4
Mirsen DWMH	3	1, 3	0	4	0-4
Mirsen PVH present	100%				
Small punctate lesions					
- hippocampus	1	1, 1	0	3	0-4
- basal ganglia	1.5	1, 2	1	4	0-4
- centrum semiovale	2	1, 3	1	4	0-4
ARWML (WM+BG)	5	4, 8	0	25	0-32

IQ range = interquartile range Med = median

PVH = Periventricular hyperintensities

DWMH = Deep white matter hyperintensities

BG = Basal ganglia

9.7 Diffusion tensor imaging

DT-MRI analyses were performed by Dr Mark E Bastin and Dr Tom J MacGillivray.

Participants underwent DT-MRI at the same scanning session as the structural scan. In the DT-MRI experiment diffusion-weighted (DW) images were acquired using a single-shot spin-echo echo-planar (EP) imaging sequence in which two symmetric trapezoidal gradient pulses of duration δ= 32.2 ms, separation Δ = 39.1 ms and rise time η = 1.2 ms were inserted around the 180° refocusing pulse in the required gradient channel. Sets of axial DW-EP images (b = 0 and 1000 s/mm^2) were collected with diffusion gradients applied sequentially along six non-collinear directions (Basser et al., 1996). Five acquisitions consisting of a baseline T2-weighted EP image and six DW-EP images, a total of 35 images, were collected per slice position. The acquisition parameters for the DW-EP imaging sequence were 21 axial slices of 5 mm thickness and 1.0 mm slice gap, a field-of-view of 240 x 240 mm, an acquisition matrix of 128 x 128 (zero filled to 256 x 256), a TR of 10 s and a TE of 98.8 ms: previously described in (Bastin et al., 2002; Shenkin, 2002).

All the DICOM format magnitude images collected in each examination were transferred from the scanner to a Sun Ultra Sparc Station 10 (Sun Microsystems, Mountain View, CA, USA) and converted into Analyze (Mayo Foundation, Rochester, MN, USA) format using `in house' software written in C. The following computations were then performed using the Matlab programming environment (The Mathworks, Natick, MA, USA).

In the DT-MRI experiment the set of five component DW-EP images for each gradient direction was averaged to give seven high signal-to-noise ratio images for each slice. Geometric image distortions arising from the strong eddy currents created by the diffusion gradients were then corrected in the six averaged DW-EP images using a modified version of the iterative cross-correlation algorithm (Bastin, Rana, Wardlaw, Armitage, & Keir, 2000). Within each voxel the six elements of **D** and the T2-weighted signal intensity were estimated by multivariate linear regression from the signal intensities measured in the DW-EP images (Basser et al., 1994). After

diagonalization of **D** to yield the magnitude sorted eigenvalues λ_1, maps of the T2-weighted signal intensity, the mean diffusivity

$$< D >= \text{Trace}(D/3) \frac{\lambda_1 + \lambda_2 + \lambda_3}{3}$$

and the fractional anisotropy (Basser, 1995)

$$FA = \sqrt{\frac{3}{2}} \sqrt{\left[\frac{(\lambda_1 - < D >)^2 + (\lambda_2 - < D >)^2 + (\lambda_3 - < D >)^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2} \right]}$$

were generated on a voxel-by-voxel basis and converted into Analyze format. The FA measures the fraction of the total `magnitude' of **D** that is anisotropic, and takes a value of 0 for isotropic diffusion ($\lambda_1 = \lambda_2 = \lambda_3$) and 1 for completely anisotropic diffusion
($\lambda_1 > 0; \lambda_2 = \lambda_3 = 0$).

A region-of-interest (ROI) analysis was then performed for normal-appearing white matter following the approach described by O'Sullivan et al (O'Sullivan et al., 2001a) (see Figure 5.1). So that the observer was not influenced by values of <D> and FA, all ROI were defined on the T2-weighted EP images. Values of <D> and FA for normal-appearing frontal and occipital periventricular white matter were obtained from multiple small circular (69 voxels, volume 303 mm^3) ROI placed near the anterior and posterior horns of the lateral ventricles. Several larger, oval ROI (typically 500 voxels, volume 2197 mm^3) were also placed in normal-appearing centrum semiovale. Partial volume effects were minimised by siting the ROI at least 3 voxels from both the edge of the ventricles and abnormally appearing white matter. Since the T2-weighted EP images and the DT-MRI parametric maps were by definition co-registered, this allowed <D> and FA values to be measured simultaneously in each ROI. Mean <D> and FA values were obtained from the average of the left and right ROI measurements made in at least two appropriate slices for each region in every subject. The observer (TJM) was blind to the clinical status and cognitive function of participants, and purpose of the study.

Intra-rater reliability: Blinded to his original ROI selection, the observer also performed an assessment of intra-rater reliability of ROI placement and editing by repeating the above analysis in ten subjects chosen at random from the study cohort. The intra-rater reliability analysis indicated excellent reproducibility of all ROI measurements, with the SD of the difference between repeated measurements of <D> being 8×10^{-6} mm^2/s (mean of measurements 774×10^{-6} mm^2/s) and FA being 0.02 (mean 0.37). This yielded coefficients of variation of 1.0 % for <D>, and 4.6 % for FA, which compares well with previous ROI studies in ageing cohorts (O'Sullivan et al., 2001b).

9.8 List of all variables

Variable name	Variable label / description
Study_no	Study ID number
datacol	Data collected
normalmr	Normal MRI? Y/N
datanote	Notes on data collected e.g. reasons for missing data etc
sex	Sex (0 = m; 1 = f)
dead	Dead? Y/N
date_dea	Date of death if known (or 01.01.year)
dob	Date of birth
datesms	Date of SMS (01.06.1932)
smsregio	Region sat SMS age 11 years
smsscore	SMS score age 11
appdate	Date of LBC appointment
appmonth	Month of LBC appointment
year	Year of LBC appointment
lbcappdt	Date of LBC appointment
whotest	Who did cognitive testing
cvhist	Cardiovascular history?
cvd	History of CVD (Y/N)
crvhist	Cerebrovascular history?
cerbvasc	History of cerebrovascular disease (Y/N)
neoplas	Neoplasia history?
cahist	History of neoplasia (Y/N)
hibp	Hypertension history?
hyphist	History of hypertension (Y/N)
diab	Diabetes history?
diabhist	History of diabetes (Y/N)
thyroid	Thyroid dysfunction history?
thyhist	History of thyroid dysfunction (Y/N)
dement	Dementia history?
demhist	History of dementia (Y/N)
othvasc	Other vascular history?
vaschist	History of other vascular problems (Y/N)
othdis	Other disease history?
othdhist	History of other diseases (Y/N)
comntdis	Comment on medical history
onmeds	On medication? (Y/N)
drug1	DRUG1
drug2	DRUG2
drug3	DRUG3
drug4	DRUG4
drug5	DRUG5
drug6	DRUG6
drug7	DRUG7
drug8	Drug 8 or more
ndrugs	Number of drugs (exclude inhalers, eye drops, gaviscon, prn meds, supplements, include GTN, ca, thiamine, vitd, vitb)
aspirin	aspirin
warfarin	warfarin
bblocker	beta blocker
aceia2a	ACE inhibitor or angiotensin II receptor antagonist
caant	calcium antagonist

diuretic	diuretic (including bendrofluazide)
statin	statin
anycv	any cardiovascular drug (bblocker, ACEI, A2A, Ca ant, bdfz, statin, GTN, digoxin, but not if frusemide or aspirin alone)
neuroact	neuroactive drug (antidepressants, benzodiazepines)
thyroxin	thyroxine
analg	regular analgesics (not including NSAIDs)
nsaid	regular NSAIDs
steroid	steroid (not creams)
antiinfl	any anti-inflammatory, ie NSAID or steroid
ohg	oral hypoglycaemics
insulin	insulin
maidn	Maiden name
married	ever married?
plborn	Place of birth
yrseduc	Number of years in full time, formal education
occ	Highest occupation of self or husband
occode	Occupational codes
soccl	Social class coded by highest reached occupation
soclcode	Social class categories
scl6code	Social class categories (III divided arbitrarially into IIIN&M)
livealn	Does person live alone?
resdnc	Type of residence
hmhlp	Number of hours per week home help visits
smoker	Is person current, ex or never smoker
stilsmk	Age still smoking as at testing
agestrt	Age started smoking
agestp	Age quit smoking
nopday	Number of cigarettes per day smoked
alcpw	Alcohol units per week (self estimate)
hada	HAD anxiety score
hadd	HAD depression score
mmse	MMSE score
mema	Story A immediate recall
memb	Story B immediate recall
mht	Moray House Test score age 80
mhtsure	Moray House Test score age 80
memdela	Story A delayed recall
memdelb	Story B delayed recall
demis	Demi-span in centimetres
height	Height in centimetres
wtkg	Weight in kilos
sit_stan	Can person stand from sitting position?
teeth	Number of teeth
yrthlost	Year all teeth were lost
sitsys	Sitting systolic pressure
sitdias	Sitting diastolic pressure
standsys	Standing systolic pressure
standdia	Standing diastolic pressure
fev	Forced expiratory volume
fvc	Forced vital capacity
fer	Forced expiratory rate
pef	Lung peak flow reading
gripstr	Dynamometer grip strength in kilos
visrun	Right eye uncorrected original chart data

vislun	Left eye uncorrected original chart data
visrcor	Right eye corrected original chart data
vislcor	Left eye corrected original chart data
ralone	Right eye row read, using 6metre standard
lalone	Left eye row read, using 6metre standard
rtcorr	Right eye corrected row read, using 6m standard
leftcor	Left eye corrected row read, using 6m standard
sixmtime	6 metre walk time
ecg	ECG performed?
rate	heart rate from ECG
axis	ECG axis
arryth	ECG arrythmia
af	Atrial fibrillation/flutter
avcond	AV conduction
vencond	Ventricular conduction
qqs	Q and QS pattern
stdepr	ST junction and segment depression
stelev	ST elevation
twave	T wave
rwave	R wave amplitude
bmgaxis	ECG axis coded by BMG
bmgarryt	ECG arrythmia coded by BMG
ecgother	ECG any other code
bmgavcon	AV conduction coded by BMG
bmgvenco	Ventricular conduction coded by BMG
bmgqqs	Q and QS pattern coded by BMG
bmgstdep	ST junction and segment depression coded by BMG
bmgstele	ST elevation coded by BMG
bmgtwave	T wave coded by BMG
bmgrwave	R wave amplitude BMG
bmgother	ECG any other code by BMG
genetic	Genetic sample taken?
blood1	blood sample successful?
blood2	blood sample successful?
blood3	blood sample successful?
towns	Townsend disability scale score
nart	NART error score
nartpos	50-NART errors
ravens	Ravens Matrices score
vfc	verbal fluency C
vff	verbal fluency F
vfl	verbal fluency L
vftot	Verbal fluency total
dateabpi	date of ABPI
testplac	place where tested for ABPI
bp	BP
r_brach	r brachial systolic pressure
l_brach	l brachial systolic pressure
r_bruit	presence of r sided bruit
l_bruit	presence of l sided bruit
r_pt	r posterior tibial systolic pressure
r_dp	r dorsalis pedis systolic pressure
l_pt	l posterior tibial systolic pressure
l_dp	l dorsalis pedis systolic pressure
result	ABPI RESULT

abpi	ABPI:lowest ankle over higher brachial decimalised
icsympt	symptoms of intermittent claudication
gait	description of gait
fields	any visual field abnormality?
fields_c	0=normal 1=homonymous hemianopia 2=bitemporal hemianopia 3=quadrantinopia 4=scotoma 5=other
eyemvmt	any problem with eye movements?
eyemvmt_	0=normal 1=R VI palsy 2=L VI palsy 3=failure of up gaze 4=failure of down gaze 5=other
nystagmu	any nystagmus?
diplopia	any complaints of diplopia?
facsens	complaints of abnormal facial sensation?
fac_wk_u	any upper facial weakness?
fac_wk_l	any lower facial weakness?
hearing	any hearing preoblems?
cough	abnormal cough?
swallow	abnormal swallow?
aah	able to say aah?
tonguemv	normal tongue movement?
dysphasi	any dysphasia?
dysarthr	any dysarthria?
tone_rul	tone right upper limb
tone_lul	tone left upper limb
tone_rll	tone right lower limb
tone_lll	tone left lower limb
power_ru	power RUL
power_lu	power LUL
power_rl	power RLL
power_ll	power LLL
refl_rb	reflex r biceps
refl_rs	reflex r supinator
refl_rt	reflex r triceps
refl_lb	reflex l biceps
refl_ls	reflex l supinator
refl_lt	reflex l triceps
refl_rk	reflex r knee
refl_ra	reflex r ankle
refl_lk	reflx l knee
refl_la	reflex l ankle
plant_r	r plantar
plant_l	l plantar
coord_ru	coordination right upper limb
coord_lu	coordination left upper limb
coord_rl	coordinaltion right lower limb
coord_ll	coordination left lower limb
fth_occ	subject's father's occupation
fthscl	father's social class (subject report of job)
fthsclcd	father's social class coded into I,II,III,IV,V
fthscl6c	father's social class with III divided into N&M
mthr_occ	subject's mother's occupation
mthocc	mother occupation
addr_11	address at age 11
rooms	number of rooms (exclude toilet/bathroom)
people	number of people sharing rooms
toilet	toilet in or outdoor
shartoil	number of people sharing toilet

fhchd	FH of coronary disease or cerebrovascular disease (m<55; f<65)
bwtrecal	subject's recollection of birth weight
mdied_ag	age of mother at death
mdied_ca	mother's cause of death
fdied_ag	age of father at death
fdied_ca	father's cause of death
notes	Notes
addcomm	Any other comments
bloodcom	Comments on blood samples
haemglob	Haemoglobin
redcells	Red cell count
haemat	Haematocrit
mcv	Mean cell volume
wcc	White cell count
neutroph	Neutrophil count
lymphocy	Lymphocyte count
monocyte	Monocyte count
eosinoph	Eosinophil count
basophil	Basophil count
platelet	Platelet count
fibrinog	Fibrinogen
vitb	B12
rcfolate	Red Cell Folate
srfolate	Serum Folate
ptt	Prothrombin time
aptt	APTT
creatini	Creatinine
hba1c	Hba1c
chol	Total serum cholesterol
triglyc	Triglycerides
tsh	TSH
freethyr	Free thyroxine
tripthy	T3 (TOTAL)
bloodnum	MRCT blood number
apoe112	ApoE 112 SNP result
apoe158	ApoE158 SNP result
apoe	ApoE genotype
apoe4yn	Possesses ApoE4 allele
apoe_suc	APOE success?
apoe_typ	APOE type
apo4car	APOE 4 carrier or not
ace_succ	ACE success
ace_type	ACE type
mth_suc	mthfr typing successful?
mthfr	MTHFR gene
doppdate	doppler date
operator	operator: EE= Mrs Elizabeth Eadie; JW= Prof Joanna Wardlaw
stenrtst	site of maximum stenosis on right ICA/CCA/other
stenrtde	degree of maximum stenosis on right
stenlfst	site of maximum stenosis on left ICA/CCA/other
stenlfde	degree of maximum stenosis on left
stencomm	comment on carotid stenosis
vertartn	is right vertebral artery normal?
vertalfn	is left vertebral artery normal?
vertacom	comment on vertebral artery

imt_rt	right intima media thickness (mm)
imt_lf	left intima media thickness (mm)
iat_rt	right intima adventitia thickness (mm)
iat_lf	left intima adventita thickness (mm)
cn	CN number from WGH for scan
id	MRI DTI id (from Mark Bastin)
wbv	Whole brain vol (mm3)
ica	Intracranial area (mm2)
cca	Corpus callosum area (mm2)
vv	Ventricular volume (mm3)
rflv	Right frontal lobe volume
lflv	Left frontal lobe volume
totflv	Total frontal lobe volume
rtlv	Right temporal lobe volume
ltlv	Left temporal lobe volume
tottlv	Total temporal lobe volume
rahcv	Right AHC volume
lahcv	Left AHC volume
totahcv	Total AHC volume
carnotes	Carly Rivers notes
atrphven	JMW coded atrophy:ventricles, scale 0-3
atrphsul	JMW coded atrophy:sulci, scale 0-3
wahlcsf	JMW coded Wahlund scale: size of CSF spaces, scale 1-3
wahlwml	JMW coded Wahlund scale: extent of WML (PVH and DWMH), scale 1-3
longst	JMW coded Longstreth scale: PVH and DWMH, scale 0-8
vanswant	JMW coded van Swieten scale anterior WM: WML in 3 slices, scale 0-2
vanswpos	JMW coded van Swieten scale posterior WM: WML in 3 slices, scale 0-2
breteler	JMW coded Breteler scale: PVH, scale 0-2
fazekpvh	JMW coded Fazekas scale, PVH: scale 0-3
fazekdwm	JMW coded Fazekas scale, DWMH: scale 0-3
shimada	JMW coded Shimada scale: PVH, scale 1-4
mirspvh	JMW coded Mirsen scale: PVH absent or present
mirsla	JMW coded Mirsen scale: DWMH, scale 0-4
gre	JMW coded gradient echo for haemorrhagic spots
smpnchp	JMW coded small punctate lesions, hippocampus, scale 0-4
smpncbg	JMW coded small punctate lesions, basal ganglia, scale 0-4
smpnccs	JMW coded small punctate lesions, centrum semiovale, scale 0-4
arwmcwm	JMW coded age related white matter changes (Wahlund), WML scale 0-3,?4 regions, 2 sides (ie 0-24)
arwmcbg	JMW coded age related white matter changes (Wahlund), basal ganglia lesions, ?scale 0-3, 2 sides (ie 0-6)
arwmltot	JMW coded ARWML WM+BG (summed manually or total as coded by JMW)
pvswmd	PVS compared to WMH
jmwcomm	JMW comments on MRI images
index	MRI index number: if >=1 then has DTI
dticomm	Comment on MRI or DTI (reasons for no data etc). Abnormality on MRI report
nf_d	Frontal mean diffusivity
nf_dstd	Frontal MD SD
nf_fa	Frontal fractional anisotropy
nf_fastd	Frontal FA SD
nf_voxel	Frontal voxels

no_d	Occipital mean diffusivity
no_dstd	Occipital MD SD
no_fa	Occipital fractional anisotropy
no_fastd	Occipital FA SD
no_voxel	Occipital voxels
cs_d	Centrum semiovale MD
cs_dstd	Centrum semiovale MD SD
cs_fa	Centrum semiovale FA
cs_fastd	Centrum semiovale FA SD
cs_voxel	Centrum semiovale voxels
birthreg	Birth Register Number from SMMP ledger
dateofad	Date of Admission to SMMP
dteofbth	Date of Birth from ledger
bthcon	Birth Condition from ledger
matage	Maternal age from ledger
prmisc	Number of Previous Miscarriages from ledger
prlab	Number of Previous Labours from ledger
pregno	Pregnancy Number from ledger
lmp	Last Menstrual Period if noted from ledger. If month only 15.x taken
deliv	Delivery mode from ledger if noted
prespos	Presentation position from ledger
complic	Complications noted in ledger
bthwtlb	Birth Weight (lbs) from ledger, or back-calculated from kg
bthwtoz	Birth weight (ozs) recorded in ledger, or back-calculated from kg
kgorlb	Birth weight recorded as kg or lbs in ledger
bthwt	Birth Weight converted to g from chart, or if originally recorded in kg
bthlen	Birth Length inches
plwtlb	Placental Weight (lbs)
plwtoz	Placental Weight (oz)
placwt	Placental Weight converted to g
placlgth	Placental Length=umbilical cord length in inches
infdisc	Infant Discharge Condition noted in ledger
disdate	Discharge Date from ledger
motforen	Mother Forename as recorded in ledger (surnames erased for confidentiality)
mthbthpl	Mother Birthplace if recorded in ledger
fathfnme	Father Forename if recorded in ledger (surnames erased for confidentiality)
patocled	Paternal Occupation if recorded in ledger
sclchk	social class checked by AP
patld6sc	Paternal Occupation if recorded in ledger with IIIN&IIM separated
illegit	Illegitimate
fdead	Father dead?
Bthaddr	Birth Address recorded in ledger
dtemarr	Marriage Date recorded in ledger
marplce	Marriage Place recorded in ledger
bthcerad	Address reported on birth certificate if different from ledger
bircerre	Birth Certificate Reference No
bthcerno	Notes from birth certificate searches
agedays	Age when seen (apptdate-dob)
ageyrs	Age in years (agedays/365.25)
agescand	age at scan in days (doppdate-dob/60*60*24)
agescany	age at scan in years (agescand/365.25)

9.9 Descriptive statistics of those who provided any data (n = 130)

The tables which follow show the descriptive statistics for the full 130 for whom any data was provided in person for the Simpson's Study (see Chapter 3), i.e. including 20 people for whom MRI was contra-indicated, who refused or were unable to undergo imaging. The results of the tests comparing the two groups (110 who underwent MRI and 20 who did not: X^2 for categorical data, Mann-Whitney U-Test for continuous data due unequal group size) are also presented.

9.9.1 Descriptive statistics

Descriptive statistics are shown in Table 9.2. Those who did not undergo MRI scanning were older and more likely to be diagnosed hypertensive. Because the study design originally aimed to recruit those born only in 1921, more intensive effort were made to collect data from those born in 1921 even though they were unable or unwilling to undergo MRI scanning.

Table 9.2 Descriptive statistics of those recruited (n = 130), and comparison between those who did and did not complete MRI scan

	n	%	Difference X^2 P
Male	40	30.8	.66
History of hypertension	63	48.5	**.036**
History of cardiovascular disease	41	31.5	.23
History of thyroid dysfunction	21	16.2	.88
History cerebrovascular disease	13	10.0	.062
History of other vascular problems	8	6.2	.44
History of neoplasia	17	13.1	.82
History of diabetes	7	5.4	.25
On medication	115	89.5	.42

	Mean	SD	Min	Max	Difference M-WU P
Age at testing (years)	78.4	1.5	75.5	82.3	**<.001***
Number of medications	3.2	2.4	0	11	.50

Bold type: P <.05 * P < .01 MW-U: Mann Whitney U test

9.9.2 Birth characteristics

Birth characteristics are shown in Table 9.3. Of the 20 who did not undergo MRI scans, 19 were born in the Royal Maternity and Simpson Memorial Hospital and one was born in the Lying-in Hospital (no birth length, gestational age or social class recorded). There were no statistically significant differences (Mann-Whitney U test or Chi squared) between this group and those who underwent an MRI scan.

Table 9.3 Birth characteristics of those recruited (n = 130), and comparison between those who did and did not complete MRI scan

Variable	n	Mean	SD	Min	Max	Difference P
Birth weight (g)	130	3331.5	461.7	2226	4564	.69
Birth length (cm)	124	50.7	2.7	43.2	55.9	.96
Placental weight (g)	94	678.8	146.2	340	1077	.94
Umbilical cord length (cm)	94	57.1	11.6	30.5	104.1	.45
Gestational age (weeks)	115	39.6	2.5	30.3	45.3	.91
Maternal age (years)	130	27.6	6.3	18	46	.14
	n	**%**				
Pregnancy number				1	9	.62
1	68	52.3				
2	29	22.3				
3	8	6.2				
4 or more	24	18.5				
Illegitimate	15	11.5				.20
Legitimate births social class						
I	2	1.5				
II	10	7.7				
IIIN	18	13.8				
IIIM	54	41.5				
IV	19	14.6				
V	12	9.2				

9.9.3 Cognitive tests

Results on cognitive tests are shown in Table 9.4. Those who did not undergo MRI scored significantly lower on logical memory and verbal fluency tests (Mann-Whitney U test). This persisted even if those with MMSE <=24, and then MMSE <=26 were excluded. Comparisons were performed on standardised residual scores corrected for age at testing in days.

Table 9.4 Cognitive test results for those recruited (n = 130) and comparison between those who did and did not complete MRI scan

Test	n	Mean	SD	Min	Max	Difference MW-U P
MMSE/30	126	28.1	1.7	18	30	.27
HAD-anxiety/21	130	5.5	3.3	0	15	.10
HAD-depression/21	130	3.9	2.3	0	15	.30
Logical Memory /100	128	31.1	12.3	6	74	**<.001***
NART (positive score) /50	130	29.5	8.2	9	44	.20
Ravens /60	123	30.1	8.6	10	51	.09
Moray House Test /76	120	56.4	10.1	17	74	.11
Verbal fluency (total)	130	36.1	12.5	6	78	**.012**

Bold type: P <.05 * P < .01

9.9.4 Physical tests

The physical test data is shown in Table 9.5. Missing data for physical variables is because most of these people were seen at home where the equipment was not available, and they were frailer and less able to perform the tests. Those who did not undergo a scan had significantly worse lung function (Mann- Whitney U test). This persisted when lung function corrected for height (FEV1 P.01; FVC P .04; PEFR P .03).

Table 9.5 Physical tests for those recruited (n = 130) and comparison between those who did and did not complete MRI scan

Variable	n	Mean	SD	Min	Max	Difference MW-U P
Weight (kg)	125	68.7	12.5	37.5	98.0	.24
Height (cm)	124	158.4	8.8	130.0	181.8	.22
Demispan (cm)	126	74.3	5.3	57.0	90.0	.58
Sitting systolic BP (mmHg)	127	158.2	25.3	99	238	.79
Sitting diastolic BP (mmHg)	127	78.5	12.7	47	124	.53
Standing systolic BP (mmHg)	123	155.7	26.5	94	244	.86
Standing diastolic BP (mmHg)	123	80.1	13.6	50	123	.86
FEV1	124	1.8	.6	.7	3.1	**.001***
FVC	124	2.3	.7	.6	4.0	**.027**
FER	124	80.9	12.3	29.0	101.0	.24
Peak flow	124	255.0	113.9	42.0	601.0	**.006***
Grip strength (kg)	124	23.5	8.2	6.0	42.0	.30
6m walk (sec)	121	5.2	2.0	2.8	14.5	1.0
ABPI	122	.91	.19	.40	1.63	.69

Bold type: P <.05 * P < .01

9.9.5 Apolipoprotein E

The Apolipoprotein E genotype frequencies are shown in Table 9.6. *APOE* allele status was determined on 123 (94.6%) of the full sample: two participants did not provide genetic material for analysis (one inpatient in hospital had no additional blood tests, one did not wish blood stored), one had insufficient blood drawn for analysis and four further samples failed on the run and no genotype could be determined.

Table 9.6 *APOE* genotypes of those recruited (n = 130)

APOE genotype	n	%
e2e2	1	0.8
e2e3	16	12.3
e2e4	5	3.8
e3e3	66	50.8
e3e4	35	26.9
Total	123	

There was no statistically significant difference in *APOE* genotype (X^2 P = .84) or rate of *APOE*e4 carriage (X^2 P = .59) between those who did and those who did not undergo MRI scan.

9.9.6 Social information

Social information is shown in Table 9.7. There was trend to shorter education in those who did not have an MRI scan (Mann-Whitney U test), and for housing, those not scanned were more likely to rent than own their own home (X^2 test).

Table 9.7 Social information for those recruited (n = 130) and comparison between those who did and did not complete MRI scan

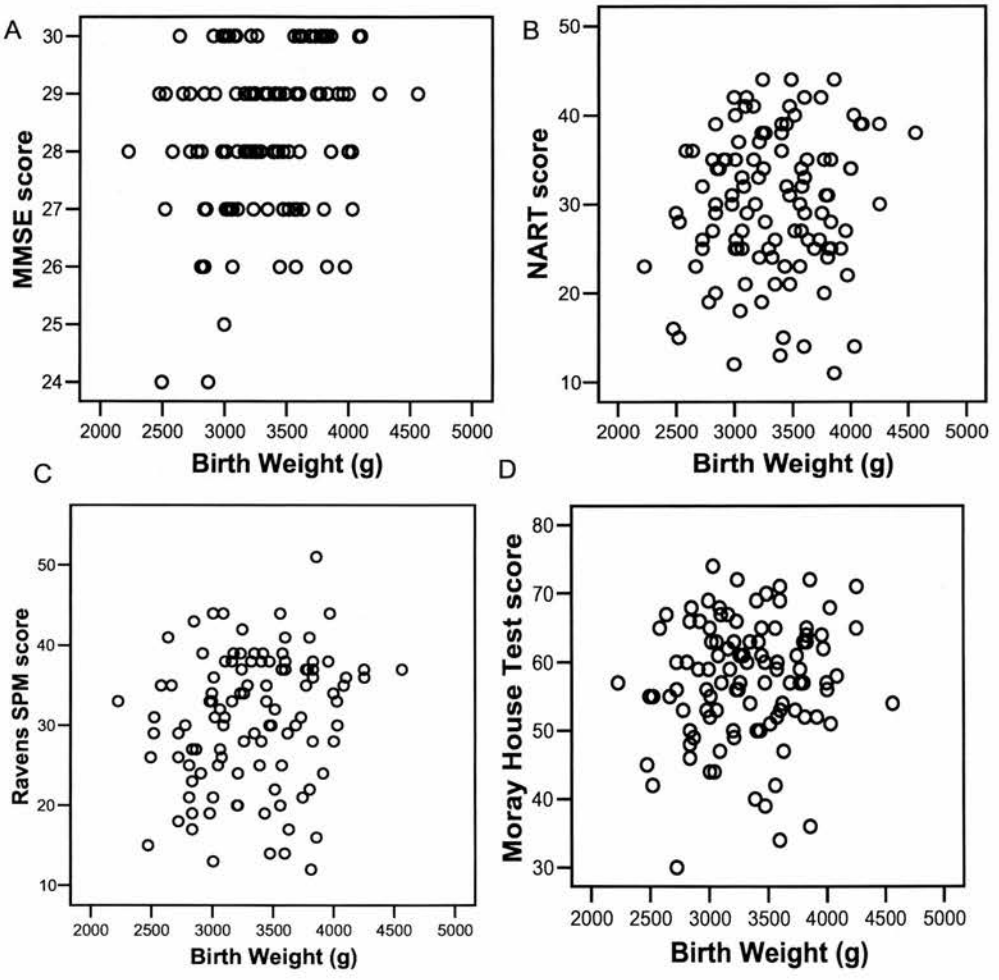
Variable	n	Median	IQ range	Min	Max	Difference P
Full-time education (yrs)	130	9.0	9.0, 11.0	7.0	22.0	.058
Alcohol per week (units)	130	1.0	1.0, 6.0	0	43.0	.27
Number of teeth	129	2.0	0, 29.0	0	29.0	.97
	n	**%**				
Lives alone	67	51.5				.74
Home help	18	13.8				
Lives in – own home	100	76.9				**.003***
- rented home	24	18.5				
- sheltered	5	3.8				
Smoking - current	12	9.2				.18
- ex	61	46.9				
- never	57	43.8				
Social class - I	10	7.7				.17
- II	39	30.0				
- IIIN	28	21.5				
- IIIM	50	38.5				
- IV	1	.8				
- V	2	1.5				.15

Bold type: P <.05 * P < .01
IQ range: interquartile range

9.10 Birth weight and cognitive ability

To examine the relationship between birth weight and cognitive ability the scatterplots of birth weight and all cognitive tests are presented (Figure 9.7). Non-parametric correlations between birth weight and cognitive tests are presented in Table 9.8.

Figure 9.7 Scatterplots of birth weight and cognitive tests around age 80 A) MMSE B) NART C) RSPM D) MHT E) Verbal fluency F) Logical Memory



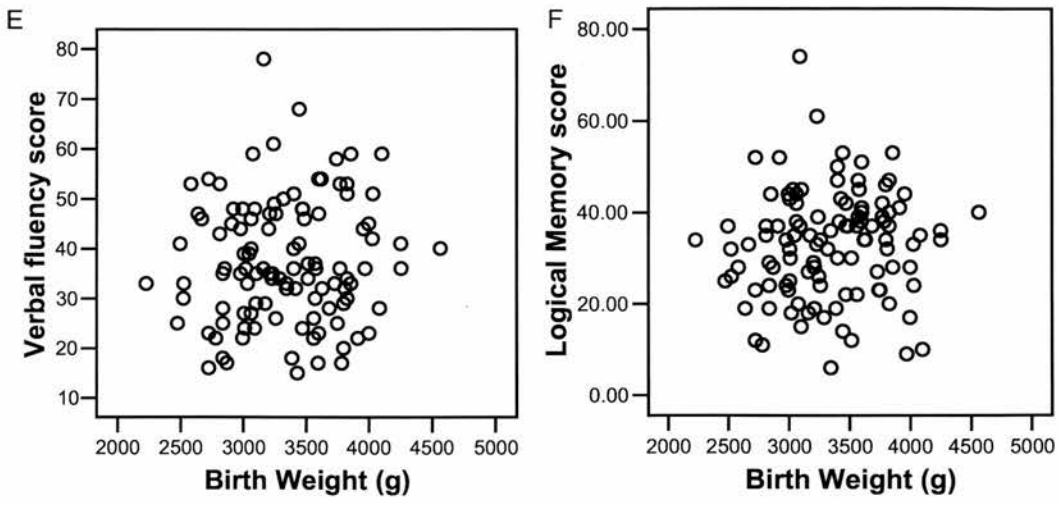


Table 9.8 Non-parametric (Spearman's ρ) correlations between birth parameters and cognitive ability in older age

	MMSE		*g*		RSPM		MHT		VF		LM		NART	
	ρ	P	ρ	P	ρ	P	ρ	P	ρ	P	ρ	P	ρ	P
BW n=110	**.23**	**.02**	.16	.11	**.21**	**.03**	.12	.21	.07	.45	.12	.19	.08	.40
BW/ GA n=100	**.21**	**.04**	**.22**	**.03**	**.26**	**.01**	.15	.14	.14	.17	.13	.20	.10	.32
BL n=107	-.10	.33	.08	.41	.06	.56	.06	.53	.08	.39	.04	.72	.08	.42
PW n = 83	.16	.14	.04	.71	.14	.22	.03	.82	-.03	.76	.08	.44	.01	.91

Bold type: P < .05

Table 9.9 shows the correlations between cognitive ability and birth weight if only births in the normal range (2500-4500g) are included.

Table 9.9: Correlations among cognitive ability in older age and birth measurements in normal birth weight individuals (n = 106)

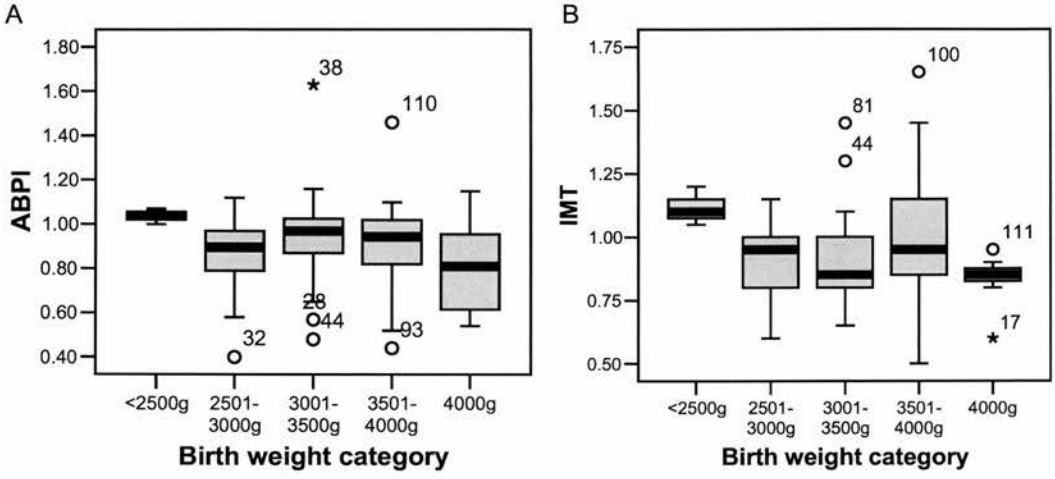
	MMSE		*g*		Ravens		MHT		VF		LM		NART	
	ρ	P	ρ	P	ρ	P	ρ	P	ρ	P	ρ	P	ρ	P
BW n=106	**.21**	**.03**	.12	.23	.18	.07	.11	.29	.05	.58	.11	.26	.02	.82
BW/ GA n=95	.18	.08	.19	.08	**.22**	**.03**	.14	.19	.12	.24	.12	.25	.03	.73
BL n=103	-.12	.22	.04	.66	.02	.87	.04	.70	.06	.53	.02	.85	.02	.81
PW n = 79	.14	.22	.00	.99	.09	.43	.00	.97	-.06	.62	.06	.58	-.04	.72

Bold type: P < .05

9.11 Birth parameters and vascular risk factors

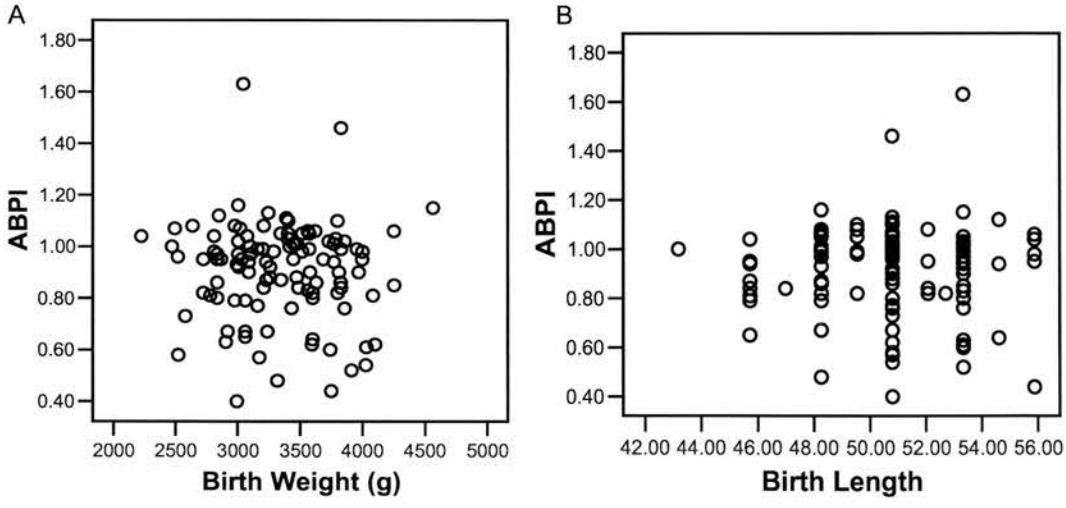
Boxplots of mean and 95% confidence intervals of birth weight for ABPI and carotid IMT are shown in Figure 9.10.

Figure 9.10 Boxplots of mean birth weight (95% CI) and ABPI (A) and carotid IMT (B)



Scatterplots of the relationship between birth parameters and ABPI are presented in Figure 9.9, and birth parameters and carotid IMT in Figure 9.10.

Figure 9.9 Scatterplots of birth parameters and ABPI
A) Birth weight B) Birth length C) Placental weight



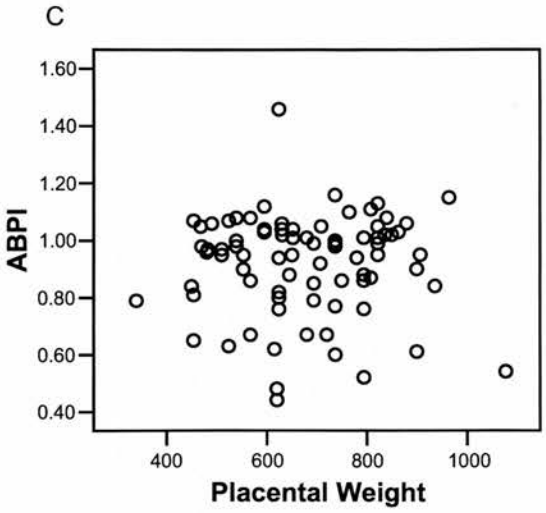
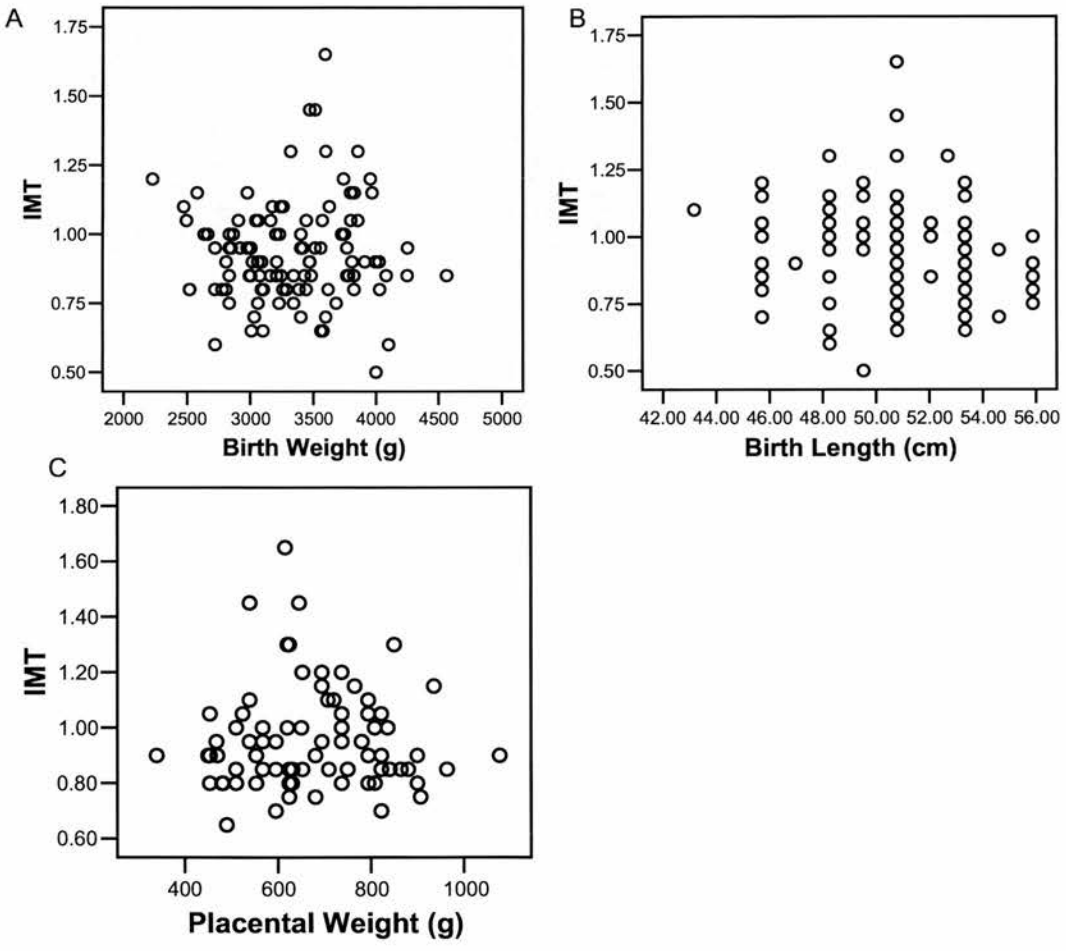


Figure 9.9 Scatterplots of birth parameters and carotid IMT Birth weight B) Birth length C) Placental weight



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